UNITED STATES PATENT AND TRADEMARK OFFICE

I, Susan POTTS BA ACIS,

Director of RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That the translator responsible for the attached translation is well acquainted with the Spanish and English languages.

3. That the attached is, to the best of RWS Group plc knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Spain on 27 July 1999 under the number P 9901694 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group plc

The 27th day of February 2002

SPANISH PATENT AND
TRADEMARK OFFICE

OFFICIAL CERTIFICATE

This is to certify that the attached documents are an exact copy of the application for a PATENT OF INVENTION number 9901694 submitted to the above Body, dated 27 July 1999.

Madrid, 12 June 2000

The Director of the Patents and
Technological Information Department
pp.

[signature]
M. MADRUGA

[seal]

SPANISH PATENT AND TRADEMARK OFFICE

[partial duty stamp]

APPLICATION NUMBER
P 9901694

FILING OF APPLICATION FOR:

☒ PATENT OF INVENTION ☐ UTILITY MODEL

DATE AND TIME OF SUBMISSION AT S.P.T.O.
27 JUL '99 13:00

DATE AND TIME OF SUBMISSION IN PLACE OTHER THAN S.P.T.O.

(1) ☐ APPLICATION FOR ADDITION
☐ DIVISIONAL APPLICATION
☐ CHANGE OF FORM
☐ EUROPEAN APPLICATION CONVERSION

(2) MAIN OR ORIGINAL FILE
FORM
APPLICATION NUMBER
DATE OF APPLICATION

FORM
APPLICATION NUMBER
DATE OF APPLICATION

(3) PLACE OF SUBMISSION
MADRID
CODE 2 8

(4) APPLICANT(S) | LAST NAMES OR LEGAL NAME | FORENAME | NID

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(5) DATA ON FIRST APPLICANT

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LOCALITY: Barcelona
PROVINCE:
COUNTRY OF RESIDENCE: Spain
NATIONALITY: Spanish

[rubber stamp]

TELEPHONE
POSTAL CODE: 08022
COUNTRY CODE: ES
NATIONAL CODE: ES

(6) INVENTOR(S)

(7) ☐ THE APPLICANT IS THE INVENTOR
☒ THE APPLICANT IS NOT THE INVENTOR OR SOLE INVENTOR

(8) METHOD OF OBTAINING THE RIGHT
☒ WORK INVEN. ☐ CONTRACT ☐ SUCCESSION

LAST NAMES	FORENAME	NATIONALITY	NATIONAL CODE
1) GRACIA FERRER	Jordi	Spanish	ES
2) FEIXAS GRAS	Joan	"	ES
3) PRIETO SOTO	José Manuel	"	ES

(9) TITLE OF THE INVENTION

"8-PHENYL-6,9-DIHYDRO[1,2,4]TRIAZOLO[3,4-i] PURIN-5-ONE DERIVATIVES"

(10) INVENTION REFERRING TO MICROBIOLOGICAL PROCESS PURSUANT TO ART. 25.2. P.A.
☐ YES ☒ NO

(11) OFFICIAL EXHIBITIONS
PLACE | DATE

(12) DECLARATIONS OF PRIORITY

COUNTRY OF ORIGIN	COUNTRY CODE	NUMBER	DATE

(13) THE APPLICANT AVAILS HIMSELF OF EXEMPTION FROM FEES REFERRED TO IN ART. 162 P.A.
☐ YES ☒ NO

(14) REPRESENTATIVE

SURNAMES	FORENAME	CODE
ELZABURU MARQUEZ	Fernando	233(X)

DOMICILE	LOCALITY	PROVINCE	POSTAL CODE
Miguel Angel, 21	MADRID	MADRID	28010

(15) LIST OF ACCOMPANYING DOCUMENTS

- ☒ DESCRIPTION, No. OF PAGES
- ☒ CLAIMS, No. OF PAGES
- ☐ DRAWINGS, No. OF PAGES
- ☒ ABSTRACT
- ☐ PRIORITY DOCUMENT
- ☐ TRANSLATION OF PRIORITY DOCUMENT
- ☒ REPRESENTATION DOCUMENT
- ☐ PROOFS
- ☒ VOUCHER FOR PAYMENT OF FEES
- ☒ ADDITIONAL INFORMATION SHEETS
- ☐ OTHERS

SIGNATURE OF THE OFFICER

SIGNATURE OF APPLICANT OR REPRESENTATIVE

[signature]
[rubber stamp: Fernando de Elzaburu
for my colleague]

(16) NOTIFICATION OF PAYMENT OF GRANT FEE

You are advised that this application shall be deemed to have been withdrawn if the grant fee is not paid: you have three months from the publication of the announcement of the grant in the OGIP, plus the ten days stipulated in Art. 81 of R.D. 10-10-86, for payment of this fee.

S.P.T.O.

HIS EXCELLENCY THE DIRECTOR OF THE SPANISH PATENT AND TRADEMARK OFFICE
PBG
UNE A-4 MOD 3101

COMPLETE THREE COPIES EXCEPT FOR THE SECTIONS MARKED IN RED

[crest] **SPANISH PATENT AND TRADEMARK OFFICE**

APPLICATION NUMBER
P9901694
DATE OF SUBMISSION
27-07-1999

ADDITIONAL INFORMATION SHEET

☒ PATENT OF INVENTION
☐ UTILITY MODEL

(4) APPLICANTS	LAST NAMES OR COMPANY NAME	FIRST NAME	NID

(5) INVENTORS	LAST NAMES	FIRST NAME	NAT.
4) VEGA NOVEROLA		Armando	ES
5) VIDAL JUAN		Bernat	ES

(11) OFFICIAL EXHIBITIONS	
PLACE:	DATE:

(12) DECLARATIONS OF PRIORITY			
COUNTRY OF ORIGIN	CODE	NUMBER	DATE

UNE A-4 MOD 3102

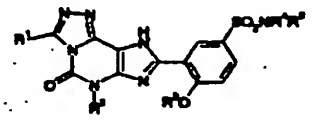
[crest]

PATENT
ABSTRACT AND DRAWING

APPLICATION NUMBER
P 9901694
DATE OF SUBMISSION
27 JUL 1999

ABSTRACT (Max. 150 words)

8-Phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives of formula (I):



(I)

wherein:

R^1, R^2 and R^3 each independently represent: hydrogen; a linear, branched or cyclic, substituted or unsubstituted, cycloaliphatic or aromatic, homocyclic or heterocyclic, organic group, R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 7- membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted; or

R^4 and R^5 independently represent a hydrogen atom, or an alkyl group which may be unsubstituted or substituted, or

R^4 represents hydrogen or an alkyl group and R^5 represents a group of formula

$$-(CH_2)_n-R^7$$

wherein n is a number from 0 to 4 and R^7 represents: an organic group; or

R^4 and R^5 represent hydroxyl, alkoxy, hydroxyalkoxy, phenyl, alkoxycarbonyl, amino, mono- or dialkylamino or hydroxycarbonyl groups; or a pharmaceutically acceptable salt thereof; processes for their preparation, pharmaceutical compositions containing them and their use as PDE 5 inhibitors.

DRAWING

SPANISH PATENT AND [crest] TRADEMARK OFFICE	PRIORITY DATA 31 NUMBER 32 DATE 33 COUNTRY	A1	12 PATENT OF INVENTION 21 APPLICATION NUMBER P 9901694 22 DATE OF SUBMISSION 27-07-1999

71 APPLICANT(S)
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73 HOLDER(S)

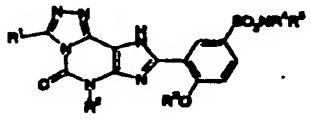
11 PUBLICATION NO.	45 DATE OF PUBLICATION	62 PATENT FROM WHICH THE PRESENT CASE IS DIVIDED OUT	DRAWING (SOLELY FOR THE PURPOSE OF INTERPRETING THE ABSTRACT)

51 INT. Cl.

54 TITLE
"8-PHENYL-6,9-DIHYDRO[1,2,4]TRIAZOLO[3,4-i]PURIN-5-ONE DERIVATIVES"

57 ABSTRACT (TO BE SUPPLIED VOLUNTARILY, WITHOUT LEGAL EFFECT)

8-Phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives of formula (I):



(I)

wherein:

R^1, R^2 and R^3 each independently represent: hydrogen; a linear, branched or cyclic, substituted or unsubstituted, cycloaliphatic or aromatic, homocyclic or heterocyclic, organic group, R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 7- membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted; or

R^4 and R^5 independently represent a hydrogen atom, or an alkyl group which may be unsubstituted or substituted, or

R^4 represents hydrogen or an alkyl group and R^5 represents a group of formula

$$-(CH_2)_n-R^7$$

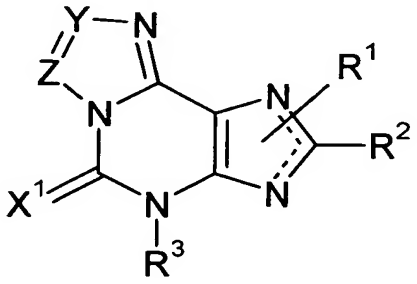
wherein n is a number from 0 to 4 and R^7 represents: an organic group; or

R^4 and R^5 represent hydroxyl, alkoxy, hydroxyalkoxy, phenyl, alkoxycarbonyl, amino, mono- or dialkylamino or hydroxycarbonyl groups; or a pharmaceutically acceptable salt thereof; processes for their preparation, pharmaceutical compositions containing them and their use as PDE 5 inhibitors.

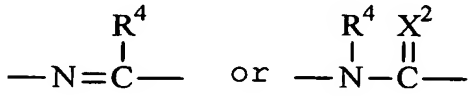
8-PHENYL-6,9-DIHYDRO[1,2,4]TRIAZOLO[3,4-*i*]PURIN-5-ONE DERIVATIVES

The present invention relates to new therapeutically useful 8-phenyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

EP 0 417 790 relates to s-triazolo[3,4-*i*]purines of general formula:



wherein Y=Z represents



where R^4 represents hydrogen, an alkyl group, an aromatic heterocyclic group which is optionally substituted with 1 or 2 substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen, or substituted or unsubstituted aryl; and X^2 represents oxygen, sulphur or NH;

each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;

R^3 represents alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;

X^1 represents oxygen or sulphur;

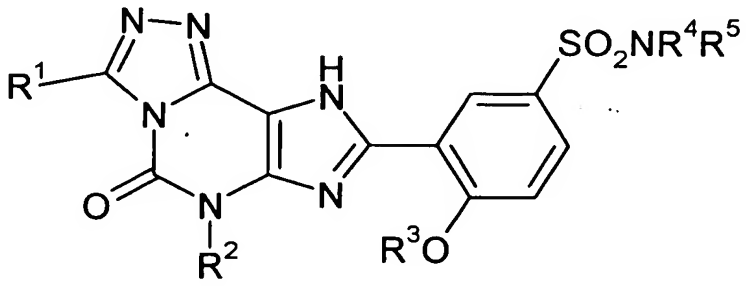
⋯ represents a single bond or a double bond and substituted or unsubstituted aryl means aryl which is

optionally substituted with 1 or 2 substituents independently selected from C_1-C_6 alkyl, trifluoromethyl, hydroxyl, C_1-C_6 alkoxyl, C_1-C_6 alkylthio, nitro, halogen, amino, C_1-C_6 alkylamino, C_1-C_6 alkanoylamino, aroylamino, carboxyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyl and aroyl;

which possess bronchodilatory activity, diuretic activity, renal protecting activity and/or antiamnesic activity.

We have now found that certain 8-(disubstituted)-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives are potent and selective inhibitors of cyclic guanosine 3'-5'-monophosphate specific phosphodiesterase (cGMP specific PDE) and more particularly inhibitors of phosphodiesterase 5 (PDE 5), and thus have utility in the treatment of angina, hypertension, congestive heart failure, thrombosis, asthma, male erectile dysfunction, female sexual dysfunction, glaucoma and irritable bowel syndrome.

Accordingly, the present invention relates to compounds which are 8-phenyl-6,9-dihydro[1,2,4]triazolo-[3,4-i]purin-5-one derivatives of formula (I):



(I)

wherein:

R^1, R^2 and R^3 each independently represent: hydrogen; an alkyl group which is unsubstituted or substituted by a hydroxyl, alkoxy, alkylthio, amino, mono- or dialkylamino, hydroxycarbonyl, alkoxycarbonyl,

acylamino, carbamoyl or alkylcarbamoyl group; or a group of formula

$$-(CH_2)_n-R^6$$

wherein n is a number from 0 to 4 and R^6 represents: a cycloalkyl group; a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, hydroxyl, alkylenedioxy, alkoxy, amino, mono- or dialkylamino, nitro, cyano or trifluoromethyl groups; or a 3- to 7- membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxyl, phenyl, alkoxycarbonyl, amino, monoalkylamino, dialkylamino or hydroxycarbonyl groups or one or more alkyl groups which may in turn be unsubstituted or substituted by one or more halogen atoms or hydroxyl, alkoxy, hydroxyalkoxy, phenyl, alkoxycarbonyl, amino, mono- or dialkylamino or hydroxycarbonyl groups;

either R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 7- membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or two halogen atoms or hydroxyl, oxoalkyl, carbamoyl, hydroxycarbonyl, alkoxycarbonyl, amino, mono- or dialkylamino groups, or one or two alkyl groups which may be unsubstituted or substituted by one or more hydroxyl, alkoxy, hydroxyalkoxy, amino or mono- or dialkylamino groups, or

R^4 and R^5 independently represent a hydrogen atom, or an alkyl group which may be unsubstituted or substituted by one or more hydroxyl, alkoxy, alkylthio, amino, mono- or dialkylamino groups, or

R^4 represents hydrogen or an alkyl group and R^5 represents a group of formula

$-(CH_2)_n-R^7$

wherein n is a number from 0 to 4 and R^7 represents: a cycloalkyl group; a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, hydroxyl, alkylenedioxy, alkoxy, amino, mono- or dialkylamino, nitro, cyano or trifluoromethyl groups; or a 3- to 7- membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxyl, alkoxy, phenyl, alkoxycarbonyl, amino, monoalkylamino, dialkylamino or hydroxycarbonyl groups or one or more alkyl groups which may be unsubstituted or substituted by one or more halogen atoms or hydroxyl, alkoxy, hydroxyalkoxy, phenyl, alkoxycarbonyl, amino, mono- or dialkylamino or hydroxycarbonyl groups;

or a pharmaceutically acceptable salt thereof.

The alkyl groups and moieties such as those present in the alkoxy, hydroxyalkoxy, alkylcarbamoyl, mono- or dialkylamino, alkylthio, alkylenedioxy and alkoxycarbonyl groups mentioned in relation to the groups R^1 to R^7 are usually "lower" alkyl, that is containing from 1 to 6, particularly from 1 to 4 carbon atoms, the hydrocarbon chain being branched or straight. Preferred alkyl groups, and where relevant alkyl moieties, include methyl, ethyl, propyl, especially n-propyl, and butyl, especially *n*-butyl. Where an alkyl group or moiety is described as being substituted by one or more substituents this preferably means from 1 to 3 substituents, more preferably one or two substituents.

The cycloalkyl groups mentioned in relation to the groups R^6 and R^7 are preferably C_{3-10} cycloalkyl groups, more preferably C_{3-7} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups.

The halogen atoms mentioned in relation to the groups R^4 to R^7 are preferably chlorine or fluorine atoms.

For compounds of the invention wherein R^1, R^2 or R^3 represent a group of formula

$$-(CH_2)_nR^6$$

n may represent 0, 1, 2, 3, or 4, preferably 0, 1 or 2.

For compounds of the present invention wherein R^6 represents a 3- to 7- membered heterocyclic ring, R^6 may be unsaturated or saturated and may represent for example a piperidyl, pyrrolidyl, azetidinyl, aziridyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, triazolyl, tetrazolyl or thienyl group, which group may be substituted or unsubstituted as defined above. In preferred compounds of the invention wherein R^1, R^2 or R^3 represent a group of formula

$$-(CH_2)_nR^6$$

and wherein R^6 represents a 3- to 7- membered heterocyclic ring, R^6 is a pyridyl, piperidyl, piperazinyl, morpholinyl, triazolyl or tetrazolyl group.

In preferred compounds of the invention R^1 represents: hydrogen; a C_1-C_4 alkyl group; or a group of formula

$$-(CH_2)_nR^6$$

wherein n is 0, 1 or 2 and R^6 represents a phenyl, pyridyl or morpholinyl group. Most preferably, R^1 represents a hydrogen atom or a methyl, ethyl, propyl, pyridyl, pyridylmethyl, benzyl or *N*-morpholinylmethyl group.

In preferred compounds of the invention R^2 represents: a C_1-C_4 alkyl group; a C_{3-10} cycloalkyl group; or a group of formula

$$-(CH_2)_nR^6$$

wherein n is 0, 1 or 2 and R^6 represents an unsubstituted or substituted phenyl group or a pyridyl group. Most preferably R^2 represents an ethyl, propyl, n-butyl, substituted or unsubstituted benzyl or 3-pyridylmethyl group.

In preferred compounds of the invention R^3 represents: a C_1-C_4 alkyl group; a C_{3-10} cycloalkyl group; or a group of formula

$$-(CH_2)_nR^6$$

wherein n is 0, 1 or 2 and R^6 represents an unsubstituted or substituted phenyl group or a pyridyl group. Most preferably R^3 represents an ethyl, propyl or n-butyl group.

For compounds of the present invention wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 7- membered ring comprising a total of from 1 to 4 heteroatoms, the ring may be saturated or unsaturated and is preferably selected from a piperidyl, pyrrolidyl, azetidinyl, aziridyl, piperazinyl, [1,4]diazepine-1-yl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, imidazolyl, imidazolidinyl, pyrazolinyl, indolinyl or isoindolinyl group, said group being unsubstituted or substituted as defined above. In

the preferred compound of the invention the ring formed by R^4, R^5 and the nitrogen atom to which they are attached is a substituted or unsubstituted piperidyl, piperazinyl, [1,4]diazepine-1-yl, morpholinyl or pyrazolyl group. Preferred substituent groups are C_1-C_4 alkyl, carbamoyl, amino, hydroxyl, formyl, hydroxy-(C_1-C_4)alkyl and hydroxyalkoxyalkyl groups wherein the alkyl moieties contain from 1 to 4 carbon atoms. Most preferably R^4 and R^5 together with the nitrogen atom to which they are attached represent a 4-hydroxypiperidyl, 4-carbamoylpiperidyl, 3-carbamoylpiperidyl, piperazinyl, 4-methylpiperazinyl, 4-ethylpiperazinyl, 4-formylpiperazinyl, 4-methyl[1,4]diazepine-1-yl, 4-(2-hydroxyethyl)-piperazinyl, 4-[2-(2-hydroxyethoxy)ethyl]piperazinyl, morpholinyl or aminopyrazolyl group.

For compounds of the invention wherein R^4 and R^5 independently represent a hydrogen atom or an alkyl group which may be unsubstituted or substituted by one or more hydroxyl, alkoxy, alkylthio, amino, mono- or dialkylamino groups, R^4 and R^5 are preferably hydrogen or a C_1-C_4 alkyl group which is unsubstituted or substituted by a hydroxyl or dimethylamino group, most preferably R^4 and R^5 independently represent hydrogen or a methyl, hydroxyethyl or dimethylaminoethyl group.

For compounds of the invention wherein R^4 is hydrogen or alkyl and R^5 represents a group of formula

$$-(CH_2)_nR^7$$

n may represent 0, 1, 2, 3, or 4, preferably 0, 1, 2 or 3.

For compound of the invention wherein R^7 represents a 3- to 7- membered heterocyclic ring, R^7 may be unsaturated or saturated and may represent for example a piperidyl, pyrrolidyl, azetidinyl, aziridyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidaz-

olyl, imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl or thienyl group, which group may be substituted or unsubstituted. In the preferred compound of the invention R^4 is hydrogen or a C_1-C_4 alkyl group and R^5 represents a group of formula

$$-(CH_2)_nR^7$$

n is 0, 1, 2 or 3 and R^7 is a pyridyl, piperidyl, piperazinyl, morpholinyl, triazolyl or tetrazolyl group. Most preferred are the compounds wherein R^4 represents hydrogen or a methyl group and R^5 represents a pyridyl, 1-morpholinylethyl, 1-piperidylethyl or 1-morpholinylpropyl group.

Of outstanding interest are:

6-ethyl-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one,

8-[2-butoxy-5-(4-methylpiperazine-1-sulphonyl)-phenyl]-6-ethyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one,

8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one,

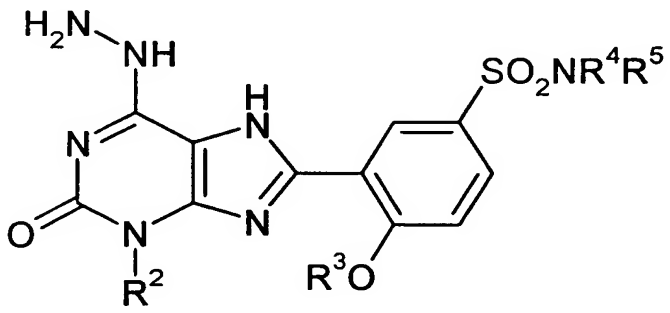
8-{5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-6-propyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one,

8-[5-(4-methyl-[1,4]diazepine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one,

6-butyl-8-{5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one, and

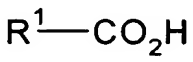
3-(5-oxo-6-propyl-6,9-dihydro-5H[1,2,4]triazolo-[3,4-*i*]purin-8-yl)-4-propoxy-*N*-pyridin-4-ylbenzenesulphonamide.

According to one feature of the present invention, the 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives of general formula (I) are prepared by reaction of the corresponding hydrazinopurine derivative of formula (II):



(II)

(wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined) with the corresponding carboxylic acid of general formula (III):

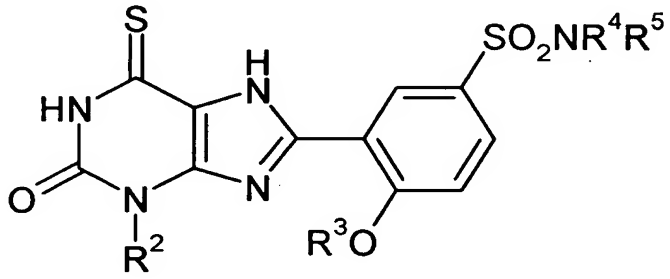


(III)

(wherein R^1 is as hereinbefore defined) or a reactive derivative thereof. Preferred Examples of a reactive derivative of the carboxylic acid (III) are the acid halide, orthoester or anhydride. The reaction may be carried out in a solvent, preferably a polar aprotic solvent, such as *N*,*N*-dimethylformamide, dioxane, acetone or tetrahydrofuran, in the presence of an organic base, preferably an amine base, such as triethylamine and at a temperature from 15°C to the boiling point of the

solvent. The reaction can also be carried out in the absence of a solvent, in which case an excess of the carboxylic acid (III) or reactive derivative of the carboxylic acid (III) is used and the mixture is heated at a temperature from 40°C to its boiling point. The thus obtained 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivative is then isolated by the usual methods known in the art.

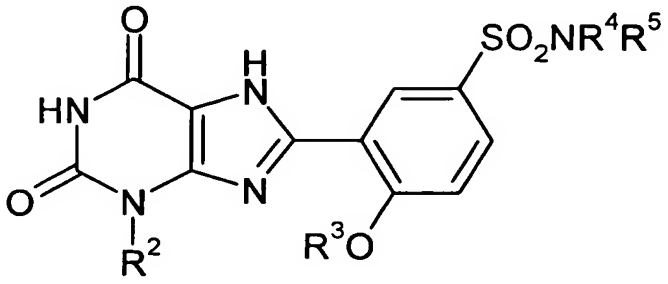
The hydrazinopurines of general formula (II) are obtained by reaction of the 6-thioxopurines of general formula(IV)



(IV)

(wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined) with hydrazine hydrate at a temperature from 80 to 150°C.

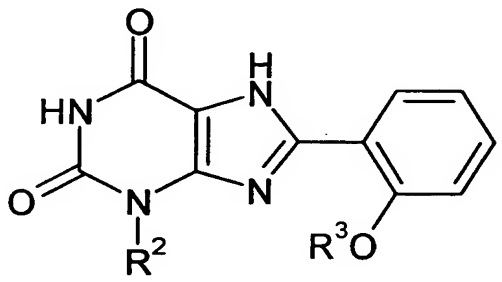
The 6-thioxopurines of general formula (IV) are obtained by reaction of the 8-phenylxanthines of general formula (V)



(V)

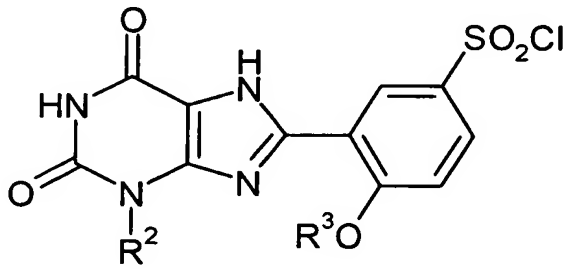
(wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined) with phosphorus pentasulphide or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide). The reaction is preferably carried out in a solvent, such as benzene, toluene, dioxane or pyridine, at a temperature from 40°C to the boiling point of the solvent.

The 8-phenylxanthines of general formula (V) are prepared from the corresponding compound of formula (VI):



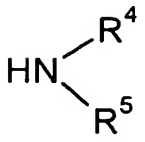
(VI)

(wherein R^2 and R^3 are as defined above) by reaction with chlorosulphonic acid (preferably in excess), preferably under a nitrogen atmosphere and at a temperature from -5°C to 10°C and where the solvent is the same chlorosulphonic acid. In this manner, the sulphonyl chloride of formula (VII):



(VII)

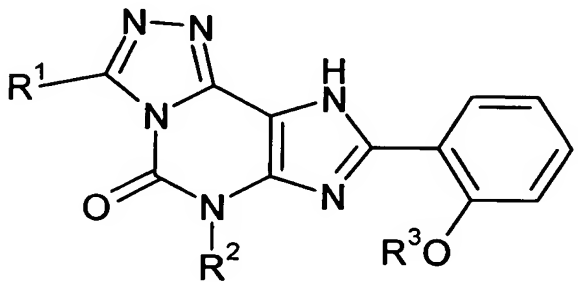
wherein R^2 and R^3 are as defined above, is obtained, which by further reaction with the corresponding amine (VIII):



(VIII)

wherein R^4 and R^5 are as defined above, produces the 8-phenylxanthine derivative of general formula (VI). The reaction is carried out in an organic solvent preferably a polar aprotic organic solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from 10°C to the boiling point of the solvent and in the presence of an organic base, preferably an amine base such as triethylamine.

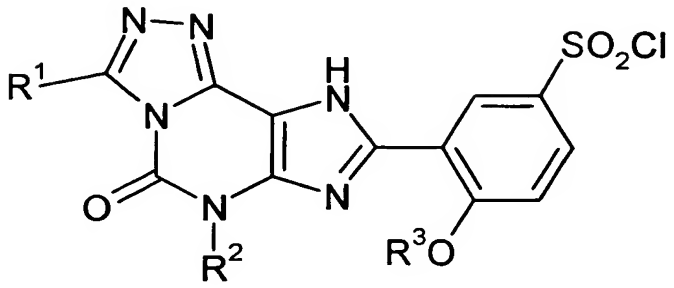
The 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one derivatives of general formula (I) are also prepared according to a further feature of the present invention, from the corresponding phenylxanthine of formula (IX):



(IX)

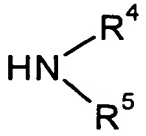
(wherein R^1, R^2 and R^3 are as hereinbefore defined) by reaction with chlorosulphonic acid (preferably in excess), preferably under a nitrogen atmosphere and at a temperature from -5°C to 10°C and where the solvent is

the same chlorosulphonic acid. In this manner, the sulphonyl chloride of formula (X):



(X)

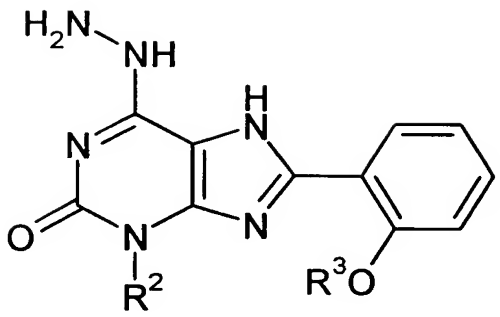
wherein R^1, R^2 and R^3 are as defined above, is obtained, which by further reaction with the corresponding amine (VIII):



(VIII)

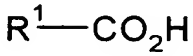
wherein R^4 and R^5 are as defined above, gives the 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivative of general formula (I). The reaction is carried out in an organic solvent preferably a polar aprotic organic solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from 10°C to 40°C and in the presence of an organic base, preferably an amine base such as triethylamine. The 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivative is then isolated by the usual methods known in the art.

The intermediate compounds of formula (IX) can be prepared by reaction of the corresponding hydrazinopurine derivative of formula (XI):



(XI)

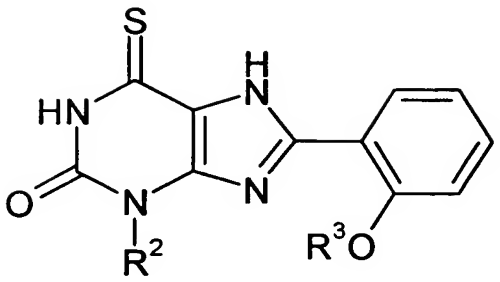
(wherein R^2 and R^3 are as hereinbefore defined) and the corresponding carboxylic acid of general formula (III):



(III)

(wherein R^1 is as hereinbefore defined) or a reactive derivative thereof. The reactive derivative of the carboxylic acid (III) is preferably an acid halide, orthoester or anhydride. The reaction can be carried out in a solvent, preferably a polar aprotic solvent, such as *N,N*-dimethylformamide, dioxane, acetone or tetrahydrofuran, in the presence of an organic base, preferably an amine base, such as triethylamine and at a temperature from 15°C to 40°C. The reaction can also be carried out in the absence of a solvent, in which case an excess of the carboxylic acid (III) or reactive derivative of the carboxylic acid (III) is used and the mixture is heated at a temperature from 40°C to its boiling point.

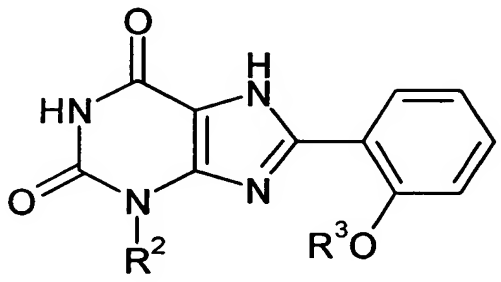
The hydrazinopurines of general formula (XI) are obtained by reaction of the 6-thioxopurines of general formula (XII)



(XII)

(wherein R^2 and R^3 are as hereinbefore defined) with hydrazine hydrate at a temperature from 80°C to 150°C.

The 6-thioxopurines of general formula (XII) are obtained by reaction of the 8-phenylxanthines of general formula (VI)



(VI)

(wherein R^2 and R^3 are as hereinbefore defined) with phosphorus pentasulphide or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide). The reaction is preferably carried out in a solvent, such as benzene, toluene, dioxane or pyridine, at a temperature from 40°C to the boiling point of the solvent.

The 8-phenylxanthines of general formula (VI) can be prepared by reaction of the corresponding 5,6-diaminouracils and the corresponding salicylic acid derivatives by methods known per se, e.g. H. W. Hamilton

et al., *J. Med. Chem.* 1985, *28*, 1071-1079 and references cited therein.

The 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives of formula (I) can be converted by methods known per se into pharmaceutically acceptable salts, preferably acid addition salts by treatment with organic or inorganic acids such as fumaric, tartaric, succinic or hydrochloric acid. Similarly, the 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives of formula (I) in which there is the presence of an acidic group may be converted into pharmacologically acceptable salts by reaction with an alkali metal hydroxide, such as sodium or potassium hydroxide, or an organic base. The acid or alkali addition salts so formed may be interchanged with suitable pharmaceutically acceptable counterions using processes known *per se*.

The cyclic GMP specific phosphodiesterase (PDE 5) was isolated from human platelet lysates by ion exchange chromatography using a Mono-Q column. The enzyme activity was determined using 0.25 µM [3H]-cyclic GMP as substrate. The purification of the enzyme and the assessment of the PDE 5 inhibitory activity of our compounds were performed essentially as described by Gristwood *et al.*, *Br. J. Pharmacol.* **1992**, *105*, 985-991. The results are shown in Table 1.

TABLE 1

Example	IC_{50} (nM)
4	11.0
6	13.0
17	1.5
18	14.0
22	3.7
27	4.0
43	4.0

As can be seen from Table 1, the compounds of formula (I) are potent inhibitors of cyclic GMP specific phosphodiesterase (PDE 5). Preferred 8-phenyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one derivatives of the invention possess an IC_{50} value for the inhibition of PDE 5 (determined as defined above) of less than 30 nM, preferably less than 20 nM and most preferably less than 15 nM. The 8-phenyl-6,9-dihydro[1,2,4]-triazolo[3,4-i]purin-5-one derivatives of the invention are useful in the treatment of stable, unstable and variant angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel potency, peripheral vascular disease, vascular disorders (e.g. Raynaud's disease), thrombosis, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, male erectile dysfunction, female sexual dysfunction and diseases characterized by disorders of gut motility, e.g. irritable bowel syndrome.

Accordingly, the 8-phenyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one derivatives of the invention and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compounds and/or salts thereof, may be used in a method of treatment of disorders of the human body which comprises administering to a patient requiring such treatment an

effective amount of a 8-phenyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one derivative of the invention or a pharmaceutically acceptable salt thereof.

The present invention also relates to pharmaceutical compositions which comprise, as active ingredient, at least one 8-phenyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one derivative of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient or diluent. The active ingredients may represent 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition, depending on the nature of the formulation and whether further dilution is to be made prior to application.

Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

The pharmaceutically acceptable excipients which are admixed with the active component, or salts of such component, to form the compositions of this invention are well known per se and the excipients used depend on the method of administering the compositions.

The compositions of this invention are preferably adapted for injectable and oral administration. In this case, the compositions for oral administration may take the form of tablets, delayed-release tablets, sublingual tablets, capsules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently

contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid compositions adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen-free aqueous media or other appropriate parenteral injection fluid.

Effective doses are normally in the range of 10-600 mg of active ingredient per day. The daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The syntheses of the compounds of the invention and of their intermediates for use therein are illustrated by the following Examples (including Preparation Examples (Preparations 1-28)) which do not limit the scope of the invention in any way.

The ^1H Nuclear Magnetic Resonance Spectra were recorded on a Varian Gemini 300 MHz spectrometer. The Mass Spectra were recorded on an HP 5988A instrument using APcI ionization. The melting points were recorded using a Perkin Elmer DSC-7 apparatus.

PREPARATION EXAMPLES

PREPARATION 1

8-(2-Ethoxyphenyl)-6-ethyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one

a) A solution of 2-ethoxybenzoyl chloride (12.0 g, 65 mmol) in dimethylformamide (10 ml) was added dropwise to a stirred solution of 5,6-diamino-1-ethyl-1*H*-pyrimidine-2,4-dione (10.4 g, 61 mmol) and triethylamine (9.8 ml, 65 mmol) in dimethylformamide (250 ml). The resulting mixture was stirred for 20 hours at room temperature, then evaporated under reduced pressure. Aqueous sodium hydroxide solution (1N, 98 ml, 98 mmol) was added and the mixture heated under reflux for 6 hours. The resulting solution was acidified with 1N hydrochloric acid and the precipitate collected and dried under vacuum to give 8-(2-ethoxyphenyl)-3-ethyl-3,7-dihydropurine-2,6-dione as a beige solid (7.0 g, 72%).

b) Phosphorus pentasulphide (5.5 g, 12.4 mmol) was added portionwise to a stirred suspension of the above compound (7.0 g, 23.3 mmol) in pyridine (115 ml) and the resulting mixture stirred under reflux for 3 hours, then evaporated under reduced pressure. The residue was triturated with hydrochloric acid (2N, 100 ml) and the precipitate collected by filtration and dried under vacuum to yield 8-(2-ethoxyphenyl)-3-ethyl-6-mercapto-3,7-dihydropurin-2-one (6.9 g, 95%) as a pale brown solid.

c) A stirred mixture of the above compound (6.9 g, 21.8 mmol) and hydrazine monohydrate (100 ml) was heated to 130°C for 3 hours. The resulting mixture was cooled and the precipitate collected by filtration and washed with water and ethanol, then dried under vacuum to yield 8-(2-ethoxyphenyl)-3-ethyl-6-hydrazino-3,7-dihydropurin-2-one (6.6 g, 97%) as an off-white solid.

d) A stirred mixture of the above compound (6.6 g, 21.0 mmol) and formic acid (110 ml) was heated under reflux for 2 hours. The resulting solution was concentrated under vacuum and the residue partitioned between dichloromethane and aqueous sodium bicarbonate

solution. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to yield the title product (5.4 g, 79%) as an off-white solid.

δ (DMSO-d6): 1.38 (3H,t), 1.49 (3H,t), 4.27 (4H,m), 7.08 (1H,t), 7.21 (1H,d), 7.47 (1H,t), 7.97 (1H,d), 9.21 (1H,s).

PREPARATION 2

4-Ethoxy-3-(6-ethyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo-[3,4-*i*]purin-8-yl)benzenesulphonyl, chloride

The title compound of Preparation 1 (5.4 g, 16.6 mmol) was added in a suitable portion to ice-cooled chlorosulphonic acid (16 ml) and the resulting mixture stirred at 0°C for 30 minutes and at room temperature overnight. The reaction mixture was carefully poured into stirred ice-water and the precipitate collected by filtration and dried under reduced pressure to yield the title compound (6.4 g, 91%) as a white solid.

δ (DMSO)-d6): 1.42 (6H,m), 4.33 (2H,q), 4.42 (2H,q), 7.23 (1H,d), 7.73 (1H,d), 8.39 (1H,s), 9.59 (1H,s).

PREPARATION 3

6-Ethyl-8-(2-propoxyphenyl)-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (51% overall) from 5,6-diamino-1-ethyl-1*H*-pyrimidine-2,4-dione and 2-propoxybenzoyl chloride by the procedure described in Preparation 1.

δ (DMSO)-d6): 1.15 (t, 3 H), 1.51 (t, 3 H), 2.05 (m, 2 H), 4.22 (t, 2 H), 4.44 (q, 2 H), 7.05 (d, 1 H), 7.12 (t, 1 H), 7.42 (t, 1 H), 8.40 (d, 1 H), 8.95 (s, 1 H), 11.40 (bs, 1 H).

PREPARATION 4

3-(6-Ethyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-4-propoxybenzenesulphonyl chloride

Obtained as a white solid (74%) from the title compound of Preparation 3, using the procedure described in Preparation 2.

δ (DMSO)-d6): 0.95 (t, 3 H), 1.39 (t, 3 H), 1.82 (m, 2 H), 4.33 (m, 4 H), 7.22 (d, 1 H), 7.75 (d, 1 H), 8.28 (s, 1 H), 9.55 (s, 1 H), 14.4 (bs, 1 H).

PREPARATION 5

8-(2-Butoxyphenyl)-6-ethyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (70% overall) from 5,6-diamino-1-ethyl-1*H*-pyrimidine-2,4-dione and 2-butoxy-benzoyl chloride by the procedure described in Preparation 1.

δ (DMSO)-d6): 1.05 (t, 3 H), 1.51 (m, 5 H), 1.95 (m, 2 H), 4.25 (t, 2 H), 4.45 (q, 2 H), 7.05 (d, 1 H), 7.13 (t, 1 H), 7.42 (t, 1 H), 8.40 (d, 1 H), 8.95 (s, 1 H), 11.55 (bs, 1 H).

PREPARATION 6

4-Butoxy-3-(6-ethyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo-[3,4-*i*]purin-8-yl)benzenesulphonyl chloride

Obtained as a white solid (42%) from the title compound of Preparation 5, using the procedure described in Preparation 2.

δ (DMSO)-d6): 0.95 (t, 3 H), 1.40 (m, 5 H), 1.80 (m, 2 H), 4.32 (m, 4 H), 7.22 (d, 1 H), 7.75 (d, 1 H), 8.38 (s, 1 H), 9.55 (s, 1 H), 13.0 (bs, 1 H).

PREPARATION 7

8-(2-Ethoxyphenyl)-6-propyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a white solid (28% overall) from 5,6-diamino-1-propyl-1*H*-pyrimidine-2,4-dione and 2-ethoxybenzoyl chloride by the procedure described in Preparation 1.

δ (DMSO)-d6): 0.96 (3H,t), 1.41 (3H,t), 1.83 (2H,m), 4.18 (2H,t), 4.28 (2H,q), 7.09 (1H,t), 7.20 (1H,d), 7.46 (1H,t), 7.93 (1H,d), 9.21 (1H,s).

PREPARATION 8

4-Ethoxy-3-(5-oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]-triazolo[3,4-*i*]purin-8-yl)benzenesulphonyl chloride

Obtained as a white solid (73%) from the title compound of Preparation 7, using the procedure described in Preparation 2.

δ (DMSO)-d6): 0.99 (3H,t), 1.42 (3H,t), 1.89 (2H,m), 4.22 (2H,t), 4.32 (2H,q), 7.19 (1H,d), 7.69 (1H,d), 8.26 (1H,s), 9.33 (1H,s).

PREPARATION 9

8-(2-Propoxyphenyl)-6-propyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a beige solid (21% overall) from 5,6-diamino-1-propyl-1*H*-pyrimidine-2,4-dione and 2-propoxybenzoyl chloride by the procedure described in Preparation 1.

δ (DMSO)-d6): 0.96 (3H,t), 0.99 (3H,t), 1.83 (4H,m), 4.17 (4H,m), 7.10 (1H,t), 7.22 (1H,d), 7.49 (1H,t), 7.96 (1H,d), 9.22 (1H,s).

PREPARATION 10

3-(5-Oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-4-propoxybenzenesulphonyl chloride

Obtained as a white solid (100%) from the title compound of Preparation 9, using the procedure described in Preparation 2.

δ (DMSO)-d6): 0.98 (6H,m), 1.88 (4H,m), 4.26 (4H,m), 7.23 (1H,d), 7.71 (1H,d), 8.30 (1H,s), 9.50 (1H,s).

PREPARATION 11

6-Butyl-8-(2-ethoxyphenyl)-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as an off-white solid (49% overall) from 5,6-diamino-1-butyl-1*H*-pyrimidine-2,4-dione and 2-ethoxybenzoyl chloride by the procedure described in Preparation 1.

δ ($CDCl_3$): 1.02 (3H,t), 1.48 (2H,m), 1.63 (3H,t), 1.88 (2H,m), 4.39 (4H,m), 7.07 (1H,d), 7.16 (1H,t), 7.42 (1H,d), 8.41 (1H,d), 8.93 (1H,s), 11.37 (1H,bs).

PREPARATION 12

3-(6-Butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-4-ethoxybenzenesulphonyl chloride

Obtained as a white solid (90%) from the title compound of Preparation 11, using the procedure described in Preparation 2.

δ ($CDCl_3$): 0.96 (3H,t), 1.42 (5H,m), 1.82 (2H,m), 4.28 (2H,t), 4.39 (2H,q), 7.20 (1H,d), 7.72 (1H,d), 8.29 (1H,s), 9.43 (1H,s).

PREPARATION 13

6-Butyl-8-(2-propoxyphenyl)-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a beige solid (41% overall) from 5,6-diamino-1-butyl-1*H*-pyrimidine-2,4-dione and 2-propoxy-benzoyl chloride by the procedure described in Preparation 1.

δ ($CDCl_3$): 1.03 (3H, t), 1.12 (3H, t), 1.50 (2H, m), 1.90 (2H, m), 2.05 (2H, m), 4.26 (2H, t), 4.39 (2H, t), 7.12 (2H, m), 7.43 (1H, t), 8.40 (1H, d), 8.95 (1H, s), 11.36 (1H, m).

PREPARATION 14

3-(6-Butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-4-propoxybenzenesulphonyl chloride

Obtained as a white solid (86%) from the title compound of Preparation 13, using the procedure described in Preparation 2.

δ ($CDCl_3$): 1.05 (6H, m), 1.50 (2H, m), 1.95 (4H, m), 4.40 (4H, m), 7.35 (1H, d), 8.10 (1H, d), 8.82 (1H, s), 9.05 (1H, s).

PREPARATION 15

8-(2-Butoxyphenyl)-6-butyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a beige solid (22% overall) from 5,6-diamino-1-butyl-1*H*-pyrimidine-2,4-dione and 2-butoxybenzoyl chloride by the procedure described in Preparation 1.

δ ($CDCl_3$): 1.02 (6H,m), 1.55 (4H,m), 1.95 (4H,m), 4.35 (4H,m), 7.10 (2H,m), 7.42 (1H,m), 8.40 (1H,d), 8.95 (1H,s), 11.43 (1H,bs).

PREPARATION 16

4-Butoxy-3-(6-butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo-[3,4-*i*]purin-8-yl)benzenesulphonyl chloride

Obtained as a white solid (77%) from the title compound of Preparation 15, using the procedure described in Preparation 2.

δ ($CDCl_3$): 1.03 (6H, m), 1.52 (4H, m), 1.95 (4H, m), 4.41 (4H, m), 7.25 (1H, d), 8.09 (1H, d), 8.95 (1H, s), 9.03 (1H, s), 11.94 (1H, bs).

PREPARATION 17

3-Methyl-8-(2-propoxyphenyl)-6-propyl-6,9-dihydro-[1,2,4]triazolo[3,4-*i*]purin-5-one

A mixture of 8-(2-propoxyphenyl)-3-propyl-6-hydrazino-3,7-dihydropurin-2-one (1.0 g, 2.9 mmol, see Preparation 9) and triethyl orthoacetate (10 ml) was heated under reflux for 2 h. The resulting mixture was cooled and the precipitate collected by filtration and washed with water and ethanol, then dried under vacuum to yield the title compound (0.82 g, 77%) as an off-white solid.

δ (DMSO)-d6): 0.92 (3H, t), 0.96 (3H, t), 1.82 (4H, m), 2.77 (3H, s), 4.24 (4H, m), 7.08 (1H, t), 7.20 (1H, d), 7.45 (1H, t), 7,92 (1H, d)

PREPARATION 18

3-(3-Methyl-5-oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]-triazolo[3,4-*i*]purin-8-yl)-4-propoxybenzenesulphonyl chloride

Obtained as a white solid (88%) from the title compound of Preparation 17, using the procedure described in Preparation 2.

δ ($CDCl_3$): 1.10 (4H, m), 1.96 (2H, m), 2.09 (2H, m), 2.96 (3H, s), 4.32 (2H, t), 4.48 (2H, t), 7.28 (1H, d), 8.09 (1H,d), 9.07 (1H, s), 11.8 (1H, bs)

PREPARATION 19

6-Hydrazino-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurin-2-one

a) Phosphorus pentasulphide (0.7 g, 3.1 mmol) was added portionwise to a stirred suspension of 8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione (1.5 g, 23.3 mmol) in pyridine (15 ml) and the resulting mixture was heated under reflux for 3 hours, then evaporated under reduced pressure to give crude 8-(2-propoxyphenyl)-3-propyl-6-mercapto-3,7-dihydropurin-2-one (1.38 g) which was used directly in the next step.

δ (DMSO)-d6): 0.89 (3H, t), 1.03 (3H, t), 1.75 (2H, m), 1.82 (2H, m), 2.15 (3H, s), 2.37 (4H, m), 2.92 (4H, m), 3.97 (2H, t), 4.20 (2H, t), 7.42 (1H, d), 7.82 (1h, d), 8.16 (1H, s), 12.34 (1H, bs), 12.67 (1H, bs).

b) A stirred mixture of the above compound (1.38 g) and hydrazine monohydrate (15 ml) was heated to 130 °C for 3 hours. The resulting mixture was cooled and the precipitate collected by filtration and washed with water and ethanol, then dried under vacuum to yield 6-hydrazino-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurin-2-one (1.08 g, 70% overall) as an off-white solid.

δ (DMSO)-d6): 0.89 (3H, t), 1.04 (3H, m), 1.70 (2H, m), 1.89 (2H, m), 2.13 (3H, s), 2.36 (4H, m), 2.91 (4H, m), 3.96 (2H,m), 4.28 (2H, m), 7.51 (1H, d), 7.81 (1H, d), 8.51 (1H, s).

PREPARATION 20

6-Hydrazino-8-[5-(piperazine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-1,3,6,7-tetrahydropurin-2-one

Obtained as a beige solid (10% overall) from 8-[5-(piperazine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione by the procedure described in Preparation 19.

δ (DMSO)-d6): 0.89 (3H, t), 1.06 (3H, m), 1.72 (2H, m), 1.91 (2H, m), 2.71 (4H, m), 2.82 (4H, m), 3.96 (2H, m), 4.28 (2H, m), 7.51 (1H, d), 7.88 (1H, d), 8.52 (1H, s).

PREPARATION 21

6-Hydrazino-8-[5-(4-methyl[1,4]diazepine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-1,3,6,7-tetrahydropurin-2-one

Obtained as an off-white solid (91% overall) from 8-[5-(4-methyl[1,4]diazepine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione by the procedure described in Preparation 19.

δ (DMSO)-d6): 0.89 (3H, t), 1.04 (3H, m), 1.72 (4H, m), 1.92 (2H, m), 2.22 (3H, s), 2.4-2.6 (6H, m), 3.38 (4H, m), 3.98 (2H, t), 4.28 (2H, t), 7.44 (1H, d), 7.86 (1H, d), 8.58 (1H, s).

PREPARATION 22

6-Hydrazino-8-[5-(morpholine-4-sulphonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurin-2-one

Obtained as a beige solid (16% overall) from 8-[5-(morpholine-4-sulphonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione by the procedure described in Preparation 19.

δ (DMSO)-d6): 0.88 (3H, t), 1.03 (3H, m), 1.75 (2H, m), 1.92 (2H, m), 2.92 (4H, m), 3.64 (4H, m), 3.96 (2H, m), 4.25 (2H, m), 7.52 (1H, m), 7.79 (1H, m), 8.51 (1H, s).

PREPARATION 23

8-[2-Butoxy-5-(4-methylpiperazine-1-sulphonyl)phenyl]-6-hydrazino-3-propyl-3,7-dihydropurin-2-one

Obtained as a beige solid (71% overall) from 8-[2-butoxy-5-(4-methylpiperazine-1-sulphonyl)phenyl]-3-propyl-3,7-dihydropurine-2,6-dione by the procedure described in Preparation 19.

δ (DMSO)-d6): 0.92 (6H,m), 1.52 (2H, m), 1.89 (4H, m), 2.12 (3H, s), 2.37 (4H, m), 2.92 (4H, m), 3.99 (2H, t), 4.26 (2H, t), 7.48 (1H, d), 7.84 (1H, d), 8.17 (1H, s).

PREPARATION 24

8-[2-Butoxy-5-(morpholine-4-sulphonyl)phenyl]-6-hydrazino-3-propyl-3,7-dihydropurin-2-one

Obtained as a beige solid (30% overall) from 8-[2-butoxy-5-(morpholine-4-sulphonyl)phenyl]-3-propyl-3,7-dihydropurine-2,6-dione by the procedure described in Preparation 19.

δ (DMSO)-d6): 0.92 (6H, m), 1.46 (2H, m), 1.68 (2H, m), 1.82 (2H, m), 2.86 (4H, m), 3.60 (4H, m), 3.94 (2H, t), 4.32 (2H, m), 7.50 (1H, d), 7.80 (1H, d), 8.49 (1H, s).

PREPARATION 25

8-(2-Propoxyphenyl)-6-pyridin-2-ylmethyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a beige solid (19% overall) from 5,6-diamino-1-pyridin-2-ylmethyl-1*H*-pyrimidine-2,4-dione and 2-propoxybenzoyl hydrochloride by the procedure described in Preparation 1.

PREPARATION 26

3-(5-Oxo-6-pyridin-2-ylmethyl-6,9-dihydro-5*H*[1,2,4]-triazolo[3,4-i]purin-8-yl)-4-propoxybenzenesulphonyl chloride

Obtained as a white solid (65%) from the title compound of Preparation 25, using the procedure described in Preparation 2.

PREPARATION 27

6-Butyl-8-(2-propoxyphenyl)-3-propyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (28% overall) from 5,6-diamino-1-butyl-1*H*-pyrimidine-2,4-dione and 2-propoxybenzoyl chloride by the procedure described in Preparation 1, using trimethyl orthobutyrate instead of formic acid in the last step.

PREPARATION 28

3-(6-Butyl-5-oxo-3-propyl-6,9-dihydro-5*H*[1,2,4]triazolo-[3,4-*i*]purin-8-yl)-4-propoxybenzenesulphonyl chloride

Obtained as a white solid (86%) from the title compound of Preparation 27, using the procedure described in Preparation 2.

PREPARATION 29

6-Isobutyl-8-(2-propoxyphenyl)-6,9-dihydro[1,2,4]-triazolo[3,4-i]purin-5-one

Obtained as a white solid (21% overall) from 5,6-diamino-1-isobutyl-1H-pyrimidine-2,4-dione and 2-propoxybenzoyl chloride by the procedure described in Preparation 1.

δ (DMSO-d6): 0.93 (9H, m), 1.80 (2H, m), 2.36 (1H, m), 4.02 (2H, d), 4.12 (2H, t), 7.09 (1H, t), 7.18 (1H, d), 7.44 (1H, t), 7.92 (1H, d), 9.20 (1H, s).

PREPARATION 30

3-(6-Isobutyl-5-oxo-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-4-propoxybenzenesulphonyl chloride

Obtained as a white solid (62%) from the title compound of Preparation 29, using the procedure described in Preparation 2.

δ (DMSO-d6): 1.01 (9H, m), 1.86 (2H, m), 2.36 (1H, m), 4.06 (2H, d), 4.19 (2H, t), 7.18 (1H, d), 7.66 (1H, d), 8.18 (1H, s), 9.27 (1H, s).

PREPARATION 31

6-Pentyl-8-(2-propoxyphenyl)-6,9-dihydro[1,2,4]-triazolo[3,4-i]purin-5-one

Obtained as a white solid (19% overall) from 5,6-diamino-1-pentyl-1H-pyrimidine-2,4-dione and 2-propoxybenzoyl chloride by the procedure described in Preparation 1.

δ (DMSO-d6): 0.83 (3H, t), 0.96 (3H, t), 1.33 (4H, m), 1.82 (4H, m), 4.15 (4H, m), 7.06 (1H, t), 7.19 (1H, d), 7.42 (1H, t), 7.91 (1H, d), 9.19 (1H, s).

PREPARATION 32

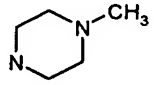
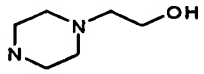
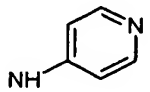
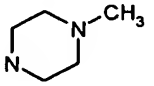
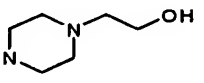
3-(5-Oxo-6-pentyl-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]-purin-8-yl)-4-propoxybenzenesulphonyl chloride

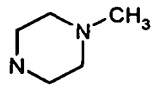
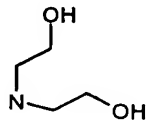
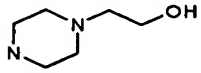
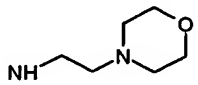
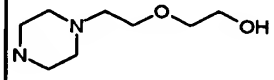
Obtained as a white solid (55%) from the title compound of Preparation 31, using the procedure described in Preparation 2.

δ (DMSO-d6): 0.88 (3H, m), 0.98 (3H, t), 1.38 (4H, m), 1.82 (4H, m), 4.26 (4H, m), 7.20 (1H, d), 7.68 (1H, d), 8.22 (1H, s), 9.38 (1H, s).

EXAMPLES

TABLE 2

Example No.	R^1	R^2	R^3	NR^4R^5
1	H	Et	Et	
2	H	Et	Et	
3	H	Et	Pr	
4	H	Et	Pr	
5	H	Et	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
6	H	Et	nBu	
7	H	Et	nBu	
8	H	Et	nBu	
9	H	Et	nBu	
10	H	Et	nBu	
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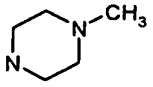
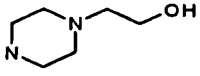
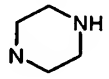
12	H	Pr	Et	
13	H	Pr	Et	

Example No.	R^1	R^2	R^3	NR^4R^5
14	H	Pr	Pr	
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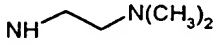
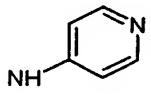
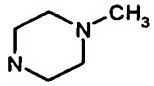
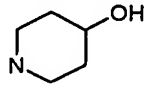
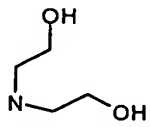
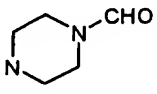
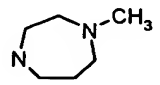
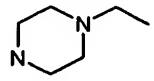
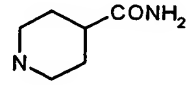
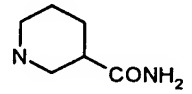
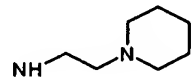
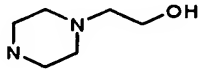
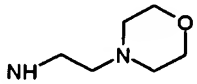
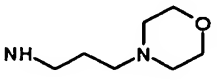
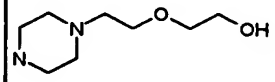
16	H	Pr	Pr	
17	H	Pr	Pr	
18	H	Pr	Pr	
19	H	Pr	Pr	
20	H	Pr	Pr	
21	H	Pr	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
22	H	Pr	Pr	
23	H	Pr	Pr	
24	H	Pr	Pr	
25	H	Pr	Pr	
26	H	Pr	Pr	
27	H	Pr	Pr	
28	H	Pr	Pr	
29	H	Pr	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
30	H	Pr	Pr	
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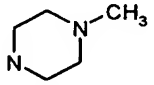
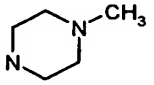
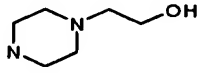
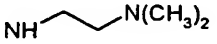
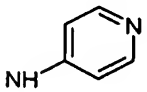
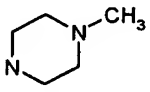
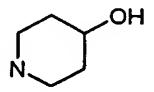
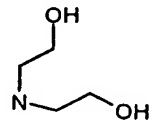
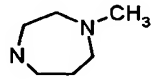
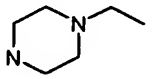
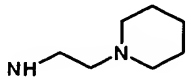
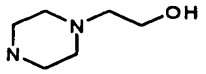
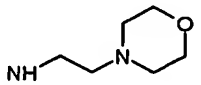
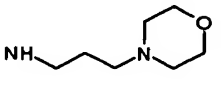
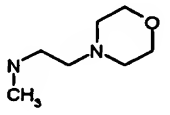
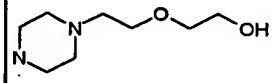
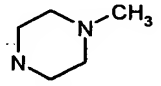
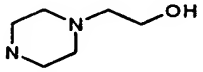
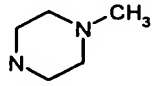
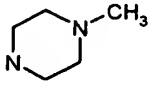
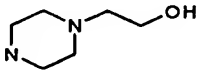
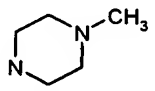
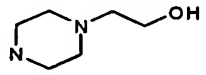
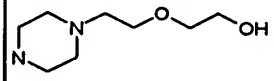
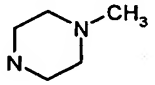
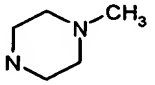
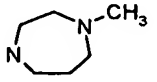
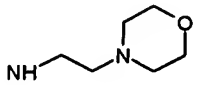
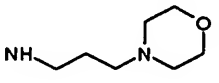
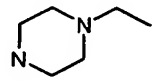
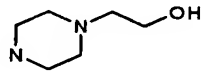
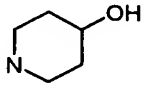
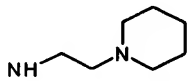
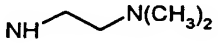
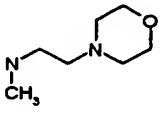
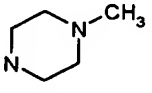
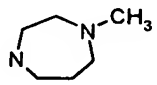
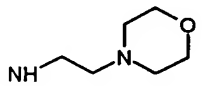
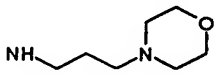
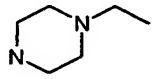
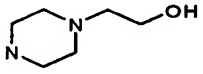
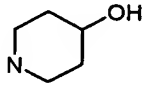
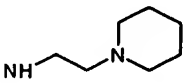
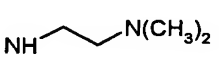
32	H	Pr	nBu	
33	H	nBu	Et	
34	H	nBu	Et	
35	H	nBu	Pr	
36	H	nBu	Pr	
37	H	nBu	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
38	H	nBu	Pr	
39	H	nBu	Pr	
40	H	nBu	Pr	
41	H	nBu	Pr	
42	H	nBu	Pr	
43	H	nBu	Pr	
44	H	nBu	Pr	
45	H	nBu	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
46	H	nBu	Pr	
47	H	nBu	Pr	
48	H	nBu	nBu	
49	H	nBu	nBu	
50	H	4-pyridyl-methyl	Pr	
51	Me	Pr	Pr	$N(CH_3)_2$
52	Me	Pr	Pr	
53	Me	Pr	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
54	Pr	nBu	Pr	
55	Pr	nBu	Pr	
56	Pr	nBu	Pr	
57	Bn	Pr	Pr	
58	H	iBu	Pr	
59	H	iBu	Pr	
60	H	iBu	Pr	
61	H	iBu	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
62	H	iBu	Pr	
63	H	iBu	Pr	
64	H	iBu	Pr	
65	H	iBu	Pr	
66	H	iBu	Pr	
67	H	iBu	Pr	
68	H	iBu	Pr	
69	H	n-Pn	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
70	H	n-Pn	Pr	
71	H	n-Pn	Pr	
72	H	n-Pn	Pr	
73	H	n-Pn	Pr	
74	H	n-Pn	Pr	
75	H	n-Pn	Pr	
76	H	n-Pn	Pr	
77	H	n-Pn	Pr	

Example No.	R^1	R^2	R^3	NR^4R^5
78	H	n-Pn	Pr	

EXAMPLE 1

8-[2-Ethoxy-5-(4-methylpiperazine-1-sulphonyl)phenyl]-6-ethyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

A solution of 1-methylpiperazine (0.3 ml, 2.6 mmol) in dichloromethane (25 ml) was added dropwise to a mixture of the title compound of Preparation 2 (1.1 g, 2.4 mmol) and triethylamine (0.4 ml, 2.6 mmol) in dichloromethane (50 ml) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, washed with an aqueous solution of sodium bicarbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude residue, on crystallization from ethanol, afforded the title compound (1.1 g, 93%) as a white solid.

m.p. 248 °C

δ (DMSO)-d6): 1.38 (3H, t), 1.50 (3H, t), 2.15 (3H, s), 2.40 (4H, m), 2.93 (4H, m), 4.25 (2H, m), 4.40 (2H, m), 7.45 (1H, d), 7.90 (1H, d), 8.24 (1H, s), 9.28 (1H, s), 13.70 (1H, bs).

EXAMPLE 2

8-{2-Ethoxy-5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]phenyl}-6-ethyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a white solid (88%) from the title compound of Preparation 2 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 230 °C

δ (DMSO)-d6): 1.40 (3H, t), 1.50 (3H, t), 2.38 (2H, t), 2.50 (4H, m), 2.90 (4H, m), 3.40 (2H, m), 4.28 (2H, m), 4.40 (3H, m), 7.46 (1H, d), 7.90 (1H, d), 8.26 (1H, s), 9.27 (1H, s), 13.65 (1H, bs).

EXAMPLE 3

6-Ethyl-8-[2-propoxy-5-(4-pyridylaminosulphonyl)]phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (46%) from the title compound of Preparation 2 and 4-aminopyridine following the procedure of Example 1.

m.p. 279 °C

δ (DMSO)-d6): 0.98 (3H, t), 1.39 (3H, t), 1.83 (2H, m), 4.19 (4H, m), 6.94 (2H, bs), 7.38 (1H, d), 7.84 (1H, d), 8.04 (2H, bs), 8.39 (1H, s), 9.22 (1H, s).

EXAMPLE 4

6-Ethyl-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (61%) from the title compound of Preparation 4 and 1-methylpiperazine following the procedure of Example 1.

m.p. 117 °C

δ (DMSO)-d6): 1.01 (3H, t), 1.37 (3H, t), 1.86 (2H, m), 2.38 (4H, m), 2.92 (4H, m), 4.26 (4H, m), 7.48 (1H, d), 7.80 (1H, d), 8.21 (1H, s), 9.28 (1H, s), 13.72 (1H, bs)

EXAMPLE 5

6-Ethyl-8-{2-propoxy-5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]phenyl}-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one

Obtained as a white solid (86%) from the title compound of Preparation 4 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 217 °C

δ (DMSO)-d6): 1.0 (3H, t), 1.37 (3H, t), 1.89 (2H, m), 2.36 (2H, t), 2.50 (2H, m), 2.79 (4H, m), 3.40 (2H, m), 4.22 (2H, t), 4.38 (1H, bs), 7.48 (1H, d), 7.82 (1H, d), 8.22 (1H, s), 9.28 (1H, s), 13.70 (1H, bs)

EXAMPLE 6

6-Ethyl-8-(2-Butoxy-5-[4-(methylpiperazine-1-sulphonyl)-phenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (56%) from the title compound of Preparation 6 and 1-methylpiperazine following the procedure of Example 1.

m.p. 206 °C

δ (DMSO)-d6): 0.94 (3H, t), 1.38 (3H, t), 1.48 (2H, m), 1.84 (2H, m), 2.16 (3H, s), 2.38 (4H, m), 2.94 (4H, m), 4.31 (4H, m), 7.80 (1H, d), 7.81 (1H, d), 8.22 (1H, s), 9.26 (1H, s), 13.71 (1H, bs)

EXAMPLE 7

4-Butoxy-3-(6-ethyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo-[3,4-*i*]purin-8-yl)-*N*,*N*-bis-(2-hydroxyethyl)benzene-sulphonamide

Obtained as a white solid (71%) from the title compound of Preparation 6 and diethanolamine following the procedure of Example 1.

m.p. 189 °C

δ (DMSO)-d6): 0.94 (3H, m), 1.39 (5H, m), 1.84 (2H, m), 3.23 (4H, m), 3.56 (4H, m), 4.29 (4H, m), 7.43 (1H, d), 7.89 (1H, d), 9.25 (1H, s).

EXAMPLE 8

6-Ethyl-8-(2-butoxy-5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]phenyl)-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one

Obtained as a white solid (54%) from the title compound of Preparation 6 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 235 °C

δ (DMSO)-d6): 0.93 (3H, t), 1.37 (3H, t), 1.45 (2H, m), 1.86 (2H, m), 2.38 (2H, t), 2.50 (4H, m), 2.91 (4H, m), 3.42 (2H, m), 4.30 (5H, m), 7.48 (1H, d), 7.80 (1H, d), 8.20 (1H, s), 9.26 (1H, s), 13.72 (1H, bs)

EXAMPLE 9

4-Butoxy-3-(6-ethyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo-[3,4-*i*]purin-8-yl)-*N*-(2-morpholin-4-ylethyl)benzene-sulphonamide

Obtained as a white solid (60%) from the title compound of Preparation 6 and *N*-(2-aminoethyl)morpholine following the procedure of Example 1.

m.p. 158 °C

δ (DMSO)-d6): 0.93 (3H, m), 1.41 (5H, m), 1.84 (2H, m), 2.30 (6H, m), 2.90 (2H, m), 3.48 (4H, m), 4.30 (4H, m), 7.43 (1H, d), 7.59 (1H, m), 7.88 (1H, d), 8.37 (1H, d), 9.26 (1H, s).

EXAMPLE 10

8-(2-Butoxy-5-{4-[2-(2-hydroxyethoxy)ethyl]piperazine-1-sulphonyl}phenyl)-6-ethyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a white solid (70%) from the title compound of Preparation 6 and 1-[2-(2-hydroxyethoxy)-ethyl]piperazine following the procedure of Example 1.

m.p. 108 °C

δ (DMSO)-d6): 0.94 (3H, m), 1.42 (5H, m), 1.83 (2H, m), 2.46 (6H, m), 2.91 (4H, m), 3.36 (6H, m), 4.32 (4H, m), 7.47 (1H, d), 7.78 (1H, d), 8.22 (1H, d), 9.27 (1H, s).

EXAMPLE 11

8-{2-Ethoxy-5-[4-morpholine-1-sulphonyl]phenyl}-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (37%) from the title compound of Preparation 8 and morpholine following the procedure of Example 1.

m.p. 265 °C

δ (DMSO)-d6): 0.95 (3H, t), 1.45 (3H, t), 1.85 (2H, m), 2.90 (4H, m), 3.65 (4H, m), 4.20 (2H, t), 4.40 (2H, c), 7.45 (1H, d), 7.80 (1H, d), 8.22 (1H, s), 9.25 (1H, s), 13.7 (1H, bs)

EXAMPLE 12

8-[2-Ethoxy-5-(4-methylpiperazine-1-sulphonyl)phenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (68%) from the title compound of Preparation 8 and 1-methylpiperazine following the procedure of Example 1.

m.p. 252 °C

δ (DMSO)-d6): 1.0 (3H, t), 1.48 (3H, t), 1.88 (2H, m), 2.19 (3H, s), 2.40 (4H, m), 2.94 (4H, m), 4.21 (2H, t), 4.41 (2H, q), 7.48 (1H, d), 7.82 (1H, d), 8.22 (1H, s), 9.28 (1H, s), 13.68 (1H, bs)

EXAMPLE 13

8-{2-Ethoxy-5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]phenyl}-6-propyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a white solid (21%) from the title compound of Preparation 8 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 223 °C

δ (DMSO)-d6): 0.98 (3H, t), 1.60 (3H, t), 1.85 (2H, m), 2.38 (2H, t), 2.50 (4H, m), 2.91 (4H, m), 3.41

(2H, m), 4.19 (2H, t), 2.39 (3H, m), 7.46 (1H, d), 7.81 (1H, d), 8.22 (1H, s), 9.28 (1H, s), 13.72 (1H, bs)

EXAMPLE 14

8-[2-Ethoxy-5-(piperazine-1-sulphonyl)phenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (25%) from the title compound of Preparation 10 and piperazine following the procedure of Example 1.

m.p. 230 °C

δ (DMSO)-d6): 0.97 (3H, t), 1.00 (3H, t), 1.86 (4H, m), 2.81 (8H, m), 4.19 (2H, t), 4.37 (2H, t), 7.46 (1H, d), 7.78 (1H, d), 8.19 (1H, s), 9.26 (1H, bs)

EXAMPLE 15

8-[5-(Morpholinosulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

A stirred mixture of the title compound of Preparation 22 (0.22 g, 0.45 mmol) and formic acid (5 ml) was heated under reflux for 2 hours. The resulting solution was concentrated under vacuum and the residue partitioned between dichloromethane and aqueous sodium bicarbonate solution. The organic phase was then separated, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product which was purified by column chromatography (SiO_2, dichloromethane-methanol 98:2) to give the title compound (0.17 g, 76%) as an off-white solid.

m.p. 169 °C

δ (DMSO)-d6): 0.98 (3H, t), 1.02 (3H, t), 1.86 (4H, m), 2.89 (4H, m), 3.61 (4H, m), 4.20 (2H,t), 4.24 (2H, t), 7.45 (1H, d), 7.82 (1H, d), 8.22 (1H, s), 9.28 (1H, s), 13.68 (1H, s)

EXAMPLE 16

N-(2-Dimethylaminoethyl)-3-(5-oxo-6-propyl-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-4-propoxybenzene-sulphonamide

Obtained as a white solid (36%) from the title compound of Preparation 10 and *N,N* -dimethylethylene-diamine following the procedure of Example 1.

MS: m/z 503 $(M+1)^+$.

δ (DMSO)-d6): 0.98 (3H, t), 1.02 (3H, t), 1.86 (4H, m), 2.89 (4H, m), 3.61 (4H, m), 4.20 (2H,t), 4.24 (2H, t), 7.45 (1H, d), 7.82 (1H, d), 8.22 (1H, s), 9.28 (1H, s), 13.68 (1H, s)

EXAMPLE 17

3-(5-Oxo-6-propyl-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]-purin-8-yl)-4-propoxy-N-pyridin-4-yl-benzenesulphonamide

Obtained as a white solid (10%) from the title compound of Preparation 10 and 4-aminopyridine following the procedure of Example 1.

m.p. 265 °C

δ (DMSO)-d6): 0.98 (3H, t), 1.02 (3H, t), 1.86 (4H, m), 2.89 (4H, m), 3.61 (4H, m), 4.20 (2H,t), 4.24 (2H, t), 7.45 (1H, d), 7.82 (1H, d), 8.22 (1H, s), 9.28 (1H, s), 13.68 (1H, s)

EXAMPLE 18

8-[5-(4-Methylpiperazinosulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (82%) from the title compound of Preparation 19 following the procedure of Example 15.

m.p. 272 °C

δ (DMSO)-d6): 0.98 (3H, t), 1.00 (3H, t), 1.83 (4H, m), 2.18 (3H, s), 2.38 (4H, m), 2.86 (4H, m), 4.19

(2H, t), 4.28 (2H, t), 7.44 (1H, d), 7.80 (1H, d), 8.19 (1H, s), 9.23 (1H, s), 13.75 (1H, bs)

EXAMPLE 19

8-[5-(4-Hydroxypiperidine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (35%) from the title compound of Preparation 10 and 4-hydroxypiperidine following the procedure of Example 1.

MS: m/z 516 $(M+1)^+$.

δ (DMSO)-d6): 0.98 (6H, m), 1.48 (2H, m), 1.74 (2H, m), 1.84 (4H, m), 2.77 (2H, m), 3.16 (2H, m), 3.60 (1H, m), 4.21 (1H, m), 4.68 (1H, s), 7.45 (1H, d), 7.78 (1H, d), 8.20 (1H, s), 9.26 (1H, s), 13.8 (1H, bs)

EXAMPLE 20

***N*,*N*-Bis-(2-hydroxyethyl)-3-(5-oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]purin-8-yl)-4-propoxybenzenesulphonamide**

Obtained as a white solid (28%) from the title compound of Preparation 10 and diethanolamine following the procedure of Example 1.

MS: m/z 520 $(M+1)^+$.

δ (DMSO)-d6): 0.97 (6H, m), 1.86 (4H, m), 3.20 (4H, t), 3.54 (4H, t), 4.20 (4H, m), 4.82 (2H, bs), 7.41 (1H, d), 7.83 (1H, d), 8.31 (1H, s), 9.23 (1H, s), 12.0 (1H, bs)

EXAMPLE 21

4-[3-(5-Oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]purin-8-yl)-4-propoxybenzenesulphonyl]piperazine-1-carbaldehyde

Obtained as a white solid (28%) from the title compound of Preparation 20 following the procedure of Example 15.

m.p. 232 °C

δ (DMSO)-d6): 0.95 (3H, t), 1.0 (3H, t), 1.86 (4H, m), 2.93 (4H, m), 3.45 (4H, m), 4.20 (2H, t), 4.24 (2H, t), 7.46 (1H, d), 7.80 (1H, d), 7.94 (1H, s), 8.20 (1H, s), 9.26 (1H, s), 13.76 (1H, s)

EXAMPLE 22

8-[5-(4-Methyl[1,4]diazepine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (32%) from the title compound of Preparation 21 following the procedure of Example 15.

m.p. 193 °C

δ (DMSO)-d6): 0.96 (3H, t), 0.98 (3H, t), 1.8 (6H, m), 2.22 (3H, s), 2.50 (2H, m), 2.58 (2H, m), 3.32 (4H, m), 4.18 (2H, t), 4.26 (2H, t), 7.40 (1H, d), 7.83 (1H, d), 8.22 (1H, s), 9.25 (1H, s)

EXAMPLE 23

8-[5-(4-Ethylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (48%) from the title compound of Preparation 10 and 1-ethylpiperazine following the procedure of Example 1.

MS: m/z 529 $(M+1)^+$.

δ (DMSO)-d6): 0.97 (9H, m), 1.83 (4H, m), 2.36 (2H, m), 2.45 (2H, m), 2.94 (4H, m), 3.35 (2H, m), 4.19 (2H, t), 4.27 (2H, t), 7.47 (1H, d), 7.80 (1H, d), 8.19 (1H, s), 9.26 (1H, s)

EXAMPLE 24

1-[3-(5-Oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]purin-8-yl)-4-propoxybenzenesulphonyl]piperidine-4-carboxamide

Obtained as a white solid (12%) from the title compound of Preparation 10 and isonipecotamide following the procedure of Example 1.

m.p. 272 °C

δ (DMSO)-d6): 0.96 (3H, t), 0.98 (3H, t), 1.58 (2H, m), 1.6-1.8 (6H, m), 2.07 (1H, m), 2.36 (2H, m), 3.57 (2H, m), 4.19 (2H, t), 4.28 (2H, t), 6.81 (1H, s), 7.20 (1H,s), 7.46 (1H, d), 7.82 (1H, d), 8.20 (1H, s), 9.27 (1H, s), 13.72 (1H, s)

EXAMPLE 25

1-[3-(5-Oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]purin-8-yl)-4-propoxybenzenesulphonyl]piperidine-3-carboxamide

Obtained as a white solid (55%) from the title compound of Preparation 10 and nipecotamide following the procedure of Example 1.

MS: m/z 543 $(M+1)^+$.

δ (DMSO)-d6): 0.97 (6H, m), 1.21 (1H, m), 1.50 (1H, m), 1.82 (6H, m), 2.26 (2H, m), 2.40 (1H, m), 3.62 (2H, m), 4.18 (2H, t), 4.27 (2H, t), 6.95 (1H, s), 7.42 (1H, s), 7.46 (1H, d), 7.80 (1H, d), 8.20 (1H, s), 9.25 (1H, s), 13.75 (1H, s)

EXAMPLE 26

3-(5-Oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-*N*-(2-piperidin-1-ylethyl)-4-propoxy-benzenesulphonamide

Obtained as a white solid (45%) from the title compound of Preparation 10 and 1-(2-aminoethyl)-piperidine following the procedure of Example 1.

MS: m/z 543 $(M+1)^+$.

δ (DMSO)-d6): 9.26 (1H, s), 8.32 (1H, s), 7.83 (1H, d), 7.62 (1H, s), 7.43 (1H, d), 4.21 (4H, m), 2.92 (2H, m), 2.41 (6H, m), 1.86 (4H, m), 1.46 (4H, m), 1.38 (2H, m), 0.97 (6H, m)

EXAMPLE 27

8-{5-[4-(2-Hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (41%) from the title compound of Preparation 10 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 194 °C

δ (DMSO)-d6): 0.95 (3H, t), 0.99 (3H, t), 1.84 (4H, m), 2.36 (2H, m), 2.50 (4H, m), 2.82 (4H, m), 3.40 (2H, m), 4.18 (2H, t), 4.28 (2H, t), 4.37 (1H, bs), 7.46 (1H, d), 7.80 (1H, d), 8.18 (1H, s), 9.26 (1H, s), 13.76 (1H, bs)

EXAMPLE 28

***N*-(2-Morpholin-4-ylethyl)-3-(5-oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]purin-8-yl)-4-propoxybenzene-sulphonamide**

Obtained as a white solid (40%) from the title compound of Preparation 10 and 4-(2-aminoethyl)-morpholine following the procedure of Example 1.

MS: m/z 545 $(M+1)^+$.

δ (DMSO)-d6): 0.97 (6H, m), 1.85 (4H, m), 2.28 (6H, m), 2.90 (2H, m), 3.48 (4H, m), 4.23 (4H, m), 7.43 (1H, d), 7.62 (1H, s), 7.90 (1H, d), 8.32 (1H, s), 9.26 (1H, s), 13.60 (1H, bs)

EXAMPLE 29

***N*-(3-Morpholin-4-ylpropyl)-3-(5-oxo-6-propyl-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]purin-8-yl)-4-propoxy-benzenesulphonamide**

Obtained as a white solid (29%) from the title compound of Preparation 10 and 4-(3-aminopropyl)morpholine following the procedure of Example 1.

MS: m/z 559 $(M+1)^+$.

δ (DMSO)-d6): 0.97 (6H, m), 1.86 (4H, m), 2.30 (6H, m), 2.81 (2H, m), 3.51 (4H, m), 4.23 (4H, m), 7.43 (1H, d), 7.63 (1H, s), 7.85 (1H, d), 8.31 (1H, s), 9.25 (1H, s)

EXAMPLE 30

8-(5-{4-[2-(2-Hydroxyethoxy)ethyl]piperazine-1-sulphonyl}-2-propoxyphenyl)-6-propyl-6,9-dihydro[1,2,4]-triazolo-[3,4-*i*]purin-5-one

Obtained as a white solid (60%) from the title compound of Preparation 10 and 1-[2-(2-hydroxyethoxy)-ethyl]piperazine following the procedure of Example 1.

m.p. 116 °C

δ (DMSO)-d6): 1.03 (6H, m), 1.84 (4H, m), 2.45 (6H, m), 2.92 (4H, m), 3.39 (6H, m), 4.21 (4H, m), 4.58 (1H, s), 7.41 (1H, d).

EXAMPLE 31

8-[2-Butoxy-5-(morpholine-4-sulphonyl)phenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (39%) from the title compound of Preparation 23 following the procedure of Example 15.

m.p. 208 °C

δ (DMSO)-d6): 0.94 (3H, t), 0.96 (3H, t), 1.48 (2H, m), 1.84 (4H, m), 2.93 (4H, m), 3.64 (4h, m), 4.20 (2H, t), 4.31 (2H, t), 7.48 (1H, d), 7.82 (1H, d), 8.20 (1H, s), 9.26 (1H, s), 13.76 (1H, s)

EXAMPLE 32

8-[5-(2-Butoxy-4-methylpiperazinosulphonyl)phenyl]-6-propyl-6,9-dihydro-1,2,4-triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (17%) from the title compound of Preparation 24 following the procedure of Example 15.

m.p. 208 °C

δ (DMSO)-d6): 0.91 (3H, t), 0.92 (3H, t), 1.43 (2H, m), 1.81 (4H, m), 2.09 (3H, s), 2.36 (4H, m), 2.88 (4H, m), 4.17 (2H, t), 4.26 (2H, t), 7.44 (1H, d), 7.79 (1H, d), 8.17 (1H, s), 9.25 (1H, s)

EXAMPLE 33

6-Butyl-8-[2-ethoxy-5-(4-methylpiperazine-1-sulphonyl)-phenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (72%) from the title compound of Preparation 12 and 1-methylpiperazine following the procedure of Example 1.

m.p. 238 °C

δ (DMSO)-d6): 0.99 (3H, t), 1.42 (5H, m), 1.82 (2H, m), 2.16 (3H, s), 2.40 (4H, m), 2.92 (4H, m), 4.22 (2H, t), 4.40 (2H, q), 7.44 (1H, d), 7.80 (1H, d), 8.22 (1H, s), 9.24 (1H, s), 13.48 (1H, s)

EXAMPLE 34

6-Butyl-8-{2-ethoxy-5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]phenyl}-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one

Obtained as a white solid (45%) from the title compound of Preparation 12 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 241 °C

δ (DMSO)-d6): 0.92 (3H, t), 1.38 (2H, m), 1.41 (3H, t), 1.80 (2H, m), 2.38 (2H, t), 2.48 (4H, m), 2.88 (4H, m), 3.40 (2H, m), 4.21 (2H, t), 4.40 (2H, q), 7.43 (1H, d), 7.80 (1H, d), 8.24 (1H, s), 9.24 (1H, s), 13.68 (1H, s).

EXAMPLE 35

3-(6-Butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-*N*-(2-dimethylaminoethyl)-4-propoxybenzene sulphonamide

Obtained as a white solid (71%) from the title compound of Preparation 14 and *N,N*-dimethylethylene-diamine following the procedure of Example 1.

m.p. 181 °C

δ (DMSO)-d6): 0.96 (6H, m), 1.37 (2H, m), 1.84 (4H, m), 2.08 (6H, s), 2.29 (2H, m), 2.86 (2H, m), 4.25 (4H, m), 7.42 (1H, d), 7.57 (1H, bs), 7.86 (1H, d), 8.34 (1H, d), 9.24 (1H, s).

EXAMPLE 36

6-Butyl-8-[2-propoxy-5-(4-pyridylaminosulphonyl)]phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (39%) from the title compound of Preparation 14 and 4-aminopyridine following the procedure of Example 1.

m.p. 282 °C

δ (DMSO)-d6): 0.97 (6H, m), 1.40 (2H, m), 1.82 (4H, m), 4.22 (4H, m), 6.97 (2H, bs), 7.38 (1H, d), 7.89 (1H, d), 8.03 (2H, bs), 8.39 (1H, s), 9.23 (1H, s).

EXAMPLE 37

6-Butyl-8-(2-propoxy-5-[4-(methylpiperazine-1-sulphonyl)phenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one

Obtained as a white solid (78%) from the title compound of Preparation 14 and 1-methylpiperazine following the procedure of Example 1.

m.p. 220 °C

δ (DMSO)-d6): 0.83 (6H, m), 1.36 (2H, m), 1.80 (4H, m), 2.12 (3H, s), 2.38 (4H, m), 2.92 (4H, m), 4.23 (4H, m), 7.45 (1H, d), 7.79 (1H, d), 8.19 (1H, s), 9.21 (1H, s), 13.69 (1H, bs).

EXAMPLE 38

6-Butyl-8-[5-(4-hydroxypiperidine-1-sulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (70%) from the title compound of Preparation 14 and 4-hydroxypiperidine following the procedure of Example 1.

m.p. 262 °C

δ (DMSO)-d6): 0.97 (6H, m), 1.41 (4H, m), 1.81 (6H, m), 2.78 (2H, m), 3.16 (2H, m), 3.55 (1H, bs), 4.24 (4H, m), 4.67 (1H, d), 7.45 (1H, d), 7.80 (1H, d), 8.23 (1H, d), 9.25 (1H, s).

EXAMPLE 39

3-(6-Butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-i]-purin-8-yl)-*N*,*N*-bis(2-hydroxyethyl)-4-propoxybenzene-sulphonamide

Obtained as a white solid (50%) from the title compound of Preparation 14 and diethanolamine following the procedure of Example 1.

m.p. 202 °C

δ (DMSO)-d6): 0.97 (6H, m), 1.38 (2H, m), 1.82 (4H, m), 3.19 (4H, m), 3.54 (4H, m), 4.25 (4H, m), 4.84 (2H, m), 7.42 (1H, d), 7.87 (1H, d), 8.29 (1H, d), 9.25 (1H, s), 13.69 (1H, s).

EXAMPLE 40

6-Butyl-8-[5-(4-methyl-[1,4]diazepine-1-sulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (39%) from the title compound of Preparation 14 and 1-methylhomopiperazine following the procedure of Example 1.

m.p. 282 °C

d ($CDCl_3$): 1.03 (3H, t), 1.14 (3H, t), 1.47 (2H, m), 1.8-2.2 (6H, m), 2.38 (3H, s), 2.68 (4H, m), 3.46 (4H, m), 4.38 (4H, m), 7.19 (1H, d), 7.86 (1H, d), 8.79 (1H, s), 8.96 (1H, s).

EXAMPLE 41

6-Butyl-8-{2-propoxy-5-[4-(ethylpiperazine-1-sulphonyl)-phenyl}-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (61%) from the title compound of Preparation 14 and 1-ethylpiperazine following the procedure of Example 1.

m.p. 208 °C

d ($CDCl_3$): 0.98 (6H, m), 1.16 (3H, t), 1.48 (2H, m), 1.91 (2H, m), 2.04 (2H, m), 2.42 (2H, q), 2.54 (4H, m), 3.13 (4H, m), 4.37 (4H, m), 7.09 (1H, d), 7.82 (1H, d), 8.77 (1H, s), 8.97 (1H, s).

EXAMPLE 42

3-(6-Butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-*N*-(2-piperidin-1-ylethyl)-4-propoxybenzene-sulphonamide

Obtained as a white solid (60%) from the title compound of Preparation 14 and 1-(2-aminoethyl)-piperidine following the procedure of Example 1.

m.p. 186 °C

δ (DMSO)-d6): 0.96 (6H, m), 1.33 (8H, m), 1.83 (4H, m), 2.28 (6H, m), 2.87 (2H, m), 4.24 (4H, m), 7.41 (1H, d), 7.51 (1H, m), 7.85 (1H, d), 8.33 (1H, d), 9.23 (1H, s).

EXAMPLE 43

6-Butyl-8-(2-propoxy-5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]phenyl}-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one

Obtained as a white solid (81%) from the title compound of Preparation 14 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 242 °C

δ (DMSO)-d6): 0.96 (3H, t), 1.0 (3H, t), 1.38 (2H, m), 1.86 (4H, m), 2.37 (2H, t), 2.50 (4H, m), 2.92 (4H, m), 3.43 (2H, m), 4.26 (4H, m), 4.37 (1H, bs), 7.47 (1H, d), 7.80 (1H, d), 8.21 (1H, s), 9.25 (1H, s), 13.70 (1H, bs).

EXAMPLE 44

3-(6-Butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-*N*-(2-morpholin-4-ylethyl)-4-propoxybenzene-sulphonamide

Obtained as a white solid (72%) from the title compound of Preparation 14 and 4-(2-aminoethyl)-morpholine following the procedure of Example 1.

m.p. 192 °C

δ (DMSO)-d6): 0.95 (6H, m), 1.38 (2H, m), 1.83 (4H, m), 2.28 (6H, m), 2.90 (2H, m), 3.46 (4H, m), 4.25 (4H, m), 7.42 (1H, d), 7.59 (1H, m), 7.87 (1H, d), 8.33 (1H, d), 9.25 (1H, s).

EXAMPLE 45

3-(6-Butyl-5-oxo-6,9-dihydro-5H[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-*N*-(3-morpholin-4-ylpropyl)-4-propoxybenzene-sulphonamide

Obtained as a white solid (65%) from the title compound of Preparation 14 and 4-(3-aminopropyl)-morpholine following the procedure of Example 1.

m.p. 174 °C

δ (DMSO)-d6): 0.96 (6H, m), 1.38 (2H, m), 1.52 (2H, m), 1.84 (4H, m), 2.21 (6H, m), 2.81 (2H, m), 3.47 (4H, m), 4.25 (4H, m), 7.43 (1H, d), 7.63 (1H, m), 7.84 (1H, d), 8.32 (1H, d), 9.25 (1H, s).

EXAMPLE 46

3-(6-Butyl-5-oxo-6,9-dihydro-5*H*[1,2,4]triazolo[3,4-*i*]-purin-8-yl)-*N*-methyl-*N*-(2-morpholin-4-ylethyl)-4-propoxybenzenesulphonamide

Obtained as a white solid (65%) from the title compound of Preparation 14 and 4-(3-aminopropyl)-morpholine following the procedure of Example 1.

m.p. 170 °C

δ (DMSO)-d6): 0.97 (6H, m), 1.38 (2H, m), 1.82 (4H, m), 2.46 (6H, m), 2.76 (3H, s), 3.12 (2H, m), 3.51 (4H, m), 4.24 (4H, m), 7.43 (1H, d), 7.84 (1H, d), 8.26 (1H, d9, 9.25 (1H, s).

EXAMPLE 47

6-Butyl-8-(5-{4-[2-(2-hydroxyethoxy)ethyl]piperazine-1-sulphonyl}-2-propoxyphenyl)-6,9-dihydro[1,2,4]triazolo-[3,4-*i*]purin-5-one

Obtained as a white solid (64%) from the title compound of Preparation 14 and 1-[2-(2-hydroxyethoxy)-ethyl]piperazine following the procedure of Example 1.

m.p. 143 °C

δ (DMSO)-d6): 0.83 (6H, m), 1.27 (2H, m), 1.68 (4H, m), 2.35 (6H, m), 2.75 (4H, m), 3.23 (6H, m), 4.11 (4H, m), 7.31 (1H, d), 7.63 (1H, d), 8.06 (1H, s), 9.10 (1H, s).

EXAMPLE 48

6-Butyl-8-(2-butoxy-5-[4-(methylpiperazine-1-sulphonyl)-phenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (62%) from the title compound of Preparation 16 and 1-methylpiperazine following the procedure of Example 1.

m.p. 201 °C

δ (DMSO)-d6): 0.98 (6H, m), 1.4 (4H, m), 1.8 (4H, m), 2.19 (3H, s), 2.4 (4H, m), 2.90 (4H, m), 4.25 (2H, t), 4.30 (2H, t), 7.45 (1H, d), 7.79 (1H,d), 8.20 (1H, s), 9.25 (1H, s), 13.65 (1H, bs)

EXAMPLE 49

6-Butyl-8-(2-butoxy-5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]phenyl}-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one

Obtained as a white solid (66%) from the title compound of Preparation 16 and 1-(2-hydroxyethyl-piperazine following the procedure of Example 1.

m.p. 218 °C

δ (DMSO)-d6): 0.95 (6H, m), 1.20 (4H, m), 1.85 (4H, m), 2.40 (2H, t), 2.51 (4H, m), 2.92 (4H, m), 3.40 (2H, m), 4.25 (5H, m), 7.48 (1H, d), 7.80 (1H, d), 8.24 (1H, s), 9.28 (1H, s), 13.65 (1H, bs).

EXAMPLE 50

8-[5-(4-Methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-pyridin-2-ylmethyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]-purin-5-one

Obtained as a white solid (82%) from the title compound of Preparation 26 and 1-methylpiperazine following the procedure of Example 1.

m.p. 227 °C

δ (DMSO)-d6): 0.93 (3H, m), 1.80 (2H, m), 2.13 (3H, s), 2.35 (4H, m), 2.87 (4H, m), 4.24 (2H, m), 5.53 (2H, m), 7.28 (1H, m), 7.44 (2H, m), 7.75 (2H, m), 8.09 (1H, d), 8.45 (1H, d), 9.31 (1H, s).

EXAMPLE 51

8-[5-(*N*,*N*-Dimethylaminosulphonyl)-2-propoxyphenyl]-3-methyl-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-2,6-dione

Obtained as a white solid (65%) from the title compound of Preparation 18 and dimethylamine following the procedure of Example 1.

m.p. 226 °C

δ (DMSO)-d6): 0.96 (3H, t), 0.98 (3H, t), 1.84 (4H, m), 2.62 (6H, s), 2.78 (3H, s), 4.16 (2H, t), 4.24 (2H, t), 7.44 (1H, d), 7.81 (1H, d), 8.21 (1H, s), 13.59 (1H, s)

EXAMPLE 52

3-Methyl-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (62%) from the title compound of Preparation 18 and 1-methylpiperazine following the procedure of Example 1.

m.p. 226 °C

δ (DMSO)-d6): 0.96 (3H, t), 0.99 (3H, t), 1.82 (4H, m), 2.16 (3H, s), 2.37 (4H, m), 2.78 (3H, s), 2.84 (4H, m), 4.14 (2H, t), 4.28 (2H, t), 7.44 (1H, d), 7.78 (1H, d), 8.19 (1H, s), 13.60 (1H, s)

EXAMPLE 53

8-{5-[4-(2-Hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-3-methyl-6-propyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (61%) from the title compound of Preparation 18 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 199 °C

δ (DMSO)-d6): 0.92 (3H, t), 0.98 (3H, t), 1.82 (4H, m), 2.38 (2H, t), 2.46 (4H, m), 2.77 (3H, s), 2.84 (4H, m), 3.39 (2H, m), 4.16 (2H, t), 4.24 (2H, t), 4.37 (1H, t), 7.43 (1H, d), 7.79 (1H, d), 8.18 (1H, s), 13.60 (1H,s)

EXAMPLE 54

6-Butyl-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-3-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Obtained as a white solid (77%) from the title compound of Preparation 28 and 1-methylpiperazine following the procedure of Example 1.

m.p. 206 °C

δ (DMSO)-d6): 0.97 (9H, m), 1.37 (2H, m), 1.81 (6H, m), 2.14 (3H, s), 2.37 (4H, m), 2.92 (4H, m), 3.19 (2H, m), 4.17 (2H, m), 4.26 (2H, m), 7.45 (1H, d), 7.79 (1H, d), 8.19 (1H, d), 13.59 (1H, bs).

EXAMPLE 55

6-Butyl-8-{5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-3-propyl-6,9-dihydro[1,2,4]triazolo-[3,4-*i*] purin-5-one

Obtained as a pale yellow solid (83%) from the title compound of Preparation 28 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

m.p. 193 °C

δ (DMSO)-d6): 0.97 (9H, m), 1.37 (2H, m), 1.81 (6H, m), 2.14 (3H, s), 2.37 (4H, m), 2.92 (4H, m), 3.19 (2H, m), 4.17 (2H, m), 4.26 (2H, m), 7.45 (1H, d), 7.79 (1H, d), 8.19 (1H, d), 13.59 (1H, bs).

EXAMPLE 56

6-Butyl-8-(5-{4-[2-(2-hydroxyethoxy)ethyl]piperazine-1-sulphonyl}-2-propoxyphenyl)-3-propyl-6,9-dihydro[1,2,4]-triazolo[3,4-*i*]purin-5-one

Obtained as a pale yellow solid (81%) from the title compound of Preparation 28 and 1-[2-(2-hydroxy-ethoxy)ethyl]piperazine following the procedure of Example 1.

m.p. 144 °C

δ (DMSO)-d6): 0.97 (9H, m), 1.38 (2H, m), 1.81 (6H, m), 2.46 (6H, m), 2.91 (4H, m), 3.19 (2H, m), 3.37 (6H, m), 4.18 (2H, m), 4.27 (2H, m), 7.45 (1H, d), 7.80 (1H, d), 8.19 (1H, d).

EXAMPLE 57

3-Benzyl-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one

Phenylacetyl chloride (0.17 ml, 1.3 mmol) was added to a mixture of the title compound of Preparation 19 (0.5 g, 1.0 mmol) and triethylamine (0.2 ml, 1.3 mmol) in dichloromethane (40 ml) and the resulting mixture was stirred at room temperature for 24 hours, then evaporated under reduced pressure. Toluene (40 ml) and a catalytic amount of p-toluenesulphonic acid were added to the residue and the resulting mixture refluxed for 2 hours using a Dean-Stark apparatus, then evaporated under reduced pressure to yield the crude product which was purified by column chromatography (SiO_2, dichloromethane-ethanol-aq. ammonia 100:4:0.5) to yield the title compound (0.11 g, 18%) as a white solid.

m.p. 202 °C

δ (DMSO)-d6): 0.92 (3H, t), 0.96 (3H, t), 1.81 (4H, m), 2.14 (3H, s), 2.37 (4H, m), 2.92 (4H, m), 4.12 (2H, t), 4.25 (2H, t), 4.65 (2H, s), 7.30 (5H, m), 7.45 (1H, d), 7.77 (1H, d), 8.17 (1H, s).

EXAMPLE 58

6-Isobutyl-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (51%) from the title compound of Preparation 30 and 1-methylpiperazine following the procedure of Example 1.

MS: m/z 528 (M+1)+.

δ (DMSO-d6): 0.94 (9H, m), 1.83 (2H, m), 2.18 (3H, s), 2.40 (1H, m), 2.45 (4H, m), 2.93 (4H, m), 4.02 (2H, d), 4.24 (2H, t), 7.44 (1H, d), 7.78 (1H, dd), 8.16 (1H, d), 9.24 (1H, s), 13.7 (1H, bs).

EXAMPLE 59

6-Isobutyl-8-[5-(4-methyl-[1,4]diazepine-1-sulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (41%) from the title compound of Preparation 30 and 1-methylhomopiperazine following the procedure of Example 1.

MS: m/z 542 (M+1)+.

δ (DMSO-d6): 1.02 (9H, m), 1.88 (5H, m), 2.48 (1H, m), 2.51 (2H, m), 2.86 (4H, m), 3.32 (4H, m), 4.05 (2H, d), 4.26 (2H, t), 7.43 (1H, d), 7.86 (1H, dd), 8.24 (1H, s), 9.27 (1H, s).

EXAMPLE 60

3-(6-Isobutyl-5-oxo-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-N-(2-morpholin-4-ylethyl)-4-propoxy-benzenesulphonamide

Obtained as a white solid (49%) from the title compound of Preparation 30 and 4-(2-aminoethyl)-morpholine following the procedure of Example 1.

MS: m/z 558 (M+1)+.

δ (DMSO-d6): 1.00 (9H, m), 1.85 (2H, m), 2.35 (6H, m), 2.94 (2H, m), 3.40 (4H, m), 4.06 (2H, d), 4.26 (2H, t), 7.43 (1H, d), 7.70 (1H, bs), 7.88 (1H, dd), 8.30 (1H, d), 9.26 (1H, s), 13.65 (1H, bs).

EXAMPLE 61

3-(6-Isobutyl-5-oxo-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-N-(3-morpholin-4-ylpropyl)-4-propoxy-benzenesulphonamide

Obtained as a white solid (29%) from the title compound of Preparation 30 and 4-(3-aminopropyl)-morpholine following the procedure of Example 1.

MS: m/z 572 (M+1)+.

δ (DMSO-d6): 1.09 (9H, m), 1.59 (2H, m), 1.85 (2H, m), 2.40 (6H, m), 2.81 (2H, m), 3.37 (4H, m), 4.06 (2H, d), 4.26 (2H, t), 7.43 (1H, d), 7.70 (1H, t), 7.85 (1H, dd), 8.30 (1H, d), 9.26 (1H, s), 13.5 (1H, bs).

EXAMPLE 62

8-[5-(4-Ethylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-isobutyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (52%) from the title compound of Preparation 30 and 1-ethylpiperazine following the procedure of Example 1.

MS: m/z 542 (M+1)+.

δ (DMSO-d6): 1.00 (12H, m), 1.86 (2H, m), 2.45 (7H, m), 2.97 (4H, m), 4.05 (2H, d), 4.27 (2H, t), 7.47 (1H, d), 7.81 (1H, dd), 8.20 (1H, d), 9.27 (1H, s), 13.7 (1H, bs).

EXAMPLE 63

8-{5-[4-(2-Hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-6-isobutyl-6,9-dihydro[1,2,4]triazolo-[3,4-i]purin-5-one

Obtained as a white solid (42%) from the title compound of Preparation 30 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

MS: m/z 558 (M+1)+.

δ (DMSO-d6): 1.00 (9H, m), 1.86 (2H, m), 2.36 (1H, m), 2.64 (4H, m), 2.99 (4H, m), 3.35 (4H, m), 4.05 (2H, d), 4.27 (2H, t), 4.56 (1H, bs), 7.47 (1H, d), 7.81 (1H, dd), 8.19 (1H, d), 9.27 (1H, s), 13.8 (1H, bs).

EXAMPLE 64

8-[5-(4-Hydroxypiperidine-1-sulphonyl)-2-propoxyphenyl]-6-isobutyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (53%) from the title compound of Preparation 30 and 4-hydroxypiperidine following the procedure of Example 1.

MS: m/z 529 (M+1)+.

δ (DMSO-d6): 0.95 (9H, m), 1.45 (2H, m), 1.79 (4H, m), 2.36 (1H, m), 2.77 (2H, m), 3.17 (2H, m), 3.55 (1H, m), 4.04 (2H, d), 4.26 (2H, t), 4.69 (1H, d), 7.45 (1H, d), 7.80 (1H, dd), 8.20 (1H, d), 9.26 (1H, s), 13.76 (1H, s).

EXAMPLE 65

3-(6-Isobutyl-5-oxo-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-N-(2-piperidin-1-ylethyl)-4-propoxy-benzenesulphonamide

Obtained as a white solid (60%) from the title compound of Preparation 30 and 1-(2-aminoethyl)-piperidine following the procedure of Example 1.

MS: m/z 556 (M+1)+.

δ (DMSO-d6): 1.00 (9H, m), 1.41 (2H, m), 1.55 (4H, m), 1.87 (2H, m), 2.38 (1H, m), 2.65 (4H, m), 3.03 (4H, m), 4.06 (2H, d), 4.27 (2H, t), 7.44 (1H, d), 7.89 (1H, dd), 7.82 (1H, bs), 8.31 (1H, d), 9.26 (1H, s).

EXAMPLE 66

N-(2-Dimethylaminoethyl)-3-(6-isobutyl-5-oxo-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-4-propoxy-benzenesulphonamide

Obtained as a white solid (43%) from the title compound of Preparation 30 and N,N-dimethylethylene-diamine following the procedure of Example 1.

MS: m/z 516 (M+1)+.

δ (DMSO-d6): 0.95 (9H, m), 1.84 (2H, m), 2.33 (1H, m), 2.33 (6H, s), 2.61 (2H, m), 2.94 (2H, m), 4.03 (2H, d), 4.23 (2H, t), 7.41 (1H, d), 7.82 (1H, bs), 7.86 (1H, dd), 8.28 (1H, d), 9.23 (1H, s).

EXAMPLE 67

6-Isobutyl-8-[5-(morpholinosulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (53%) from the title compound of Preparation 30 and morpholine following the procedure of Example 1.

MS: m/z 515 (M+1)+.

δ (DMSO-d6): 0.96 (9H, m), 1.83 (2H, m), 2.33 (1H, m), 2.88 (4H, m), 3.62 (4H, m), 4.02 (2H, d), 4.24 (2H, t), 7.45 (1H, d), 7.78 (1H, d), 8.16 (1H, s), 9.23 (1H, s), 13.77 (1H, s).

EXAMPLE 68

3-(6-Isobutyl-5-oxo-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-N-methyl-N-(2-morpholin-4-ylethyl)-4-propoxybenzenesulphonamide

Obtained as a white solid (53%) from the title compound of Preparation 30 and 4-[2-(N-methylamino)-ethyl]morpholine following the procedure of Example 1.

MS: m/z 572 (M+1)+.

δ (DMSO-d6): 0.94 (9H, m), 1.84 (2H, m), 2.41 (6H, m), 2.74 (3H, s), 3.11 (2H, m), 3.52 (4H, m), 4.01 (2H, d), 4.23 (2H, t), 7.41 (1H, d), 7.83 (1H, d), 8.22 (1H, s), 9.23 (1H, s).

EXAMPLE 69

8-[5-(4-Methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-pentyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (35%) from the title compound of Preparation 32 and 1-methylpiperazine following the procedure of Example 1.

MS: m/z 542 (M+1)+.

δ (DMSO-d6): 0.85 (3H, t), 0.97 (3H, t), 1.33 (4H, m), 1.83 (4H, m), 2.25 (3H, s), 2.48 (4H, m), 2.96 (4H, m), 4.22 (4H, m), 7.45 (1H, d), 7.78 (1H, d), 8.20 (1H, s), 9.24 (1H, s), 13.7 (1H, bs).

EXAMPLE 70

8-[5-(4-Methyl-[1,4]diazepine-1-sulphonyl)-2-propoxy-phenyl]-6-pentyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (40%) from the title compound of Preparation 32 and 1-methylhomopiperazine following the procedure of Example 1.

MS: m/z 556 (M+1)+.

δ (DMSO-d6): 0.89 (3H, t), 1.02 (3H, t), 1.37 (4H, m), 1.85 (7H, m), 2.50 (2H, m), 2.98 (4H, m), 3.32 (4H, m), 4.23 (4H, m), 7.44 (1H, d), 7.86 (1H, dd), 8.27 (1H, d), 9.26 (1H, s).

EXAMPLE 71

N-(2-Morpholin-4-ylethyl)-3-(5-oxo-6-pentyl-6,9-dihydro5H[1,2,4]triazolo[3,4-i]purin-8-yl)-4-propoxy-benzenesulphonamide

Obtained as a white solid (32%) from the title compound of Preparation 32 and 4-(2-aminoethyl)-morpholine following the procedure of Example 1.

MS: m/z 572 (M+1)+.

δ (DMSO-d6): 0.90 (3H, t), 0.98 (3H, t), 1.36 (4H, m), 1.86 (4H, m), 2.41 (6H, m), 2.94 (2H, m), 3.53 (4H, m), 4.25 (4H, m), 7.43 (1H, d), 7.68 (1H, bs), 7.88 (1H, dd), 8.33 (1H, d), 8.26 (1H, s), 13.65 (1H, bs).

EXAMPLE 72

N-(3-Morpholin-4-ylpropyl)-3-(5-oxo-6-pentyl-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-4-propoxy-benzenesulphonamide

Obtained as a white solid (38%) from the title compound of Preparation 32 and 4-(3-aminopropyl)-morpholine following the procedure of Example 1.

MS: m/z 586 (M+1)+.

δ (DMSO-d6): 0.87 (3H, t), 0.95 (3H, t), 1.37 (4H, m), 1.61 (2H, m), 1.85 (4H, m), 2.44 (6H, m), 2.81 (2H, m), 3.38 (4H, m), 4.25 (4H, m), 7.44 (1H, d), 7.69 (1H, bs), 7.85 (1H, dd), 8.32 (1H, d), 9.26 (1H, s), 13.6 (1H, bs).

EXAMPLE 73

8-[5-(4-Ethylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-pentyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (35%) from the title compound of Preparation 32 and 1-ethylpiperazine following the procedure of Example 1.

MS: m/z 556 (M+1)+.

δ (DMSO-d6): 0.90 (3H, t), 1.00 (6H, m), 1.38 (4H, m), 1.85 (4H, m), 2.49-3.07 (10H, m), 4.22 (2H, t), 4.29 (2H, t), 7.48 (1H, d), 7.81 (1H, dd), 8.23 (1H, d), 9.27 (1H, s), 13.75 (1H, bs).

EXAMPLE 74

8-{5-[4-(2-Hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-6-pentyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (33%) from the title compound of Preparation 32 and 1-(2-hydroxyethyl)-piperazine following the procedure of Example 1.

MS: m/z 572 (M+1)+.

δ (DMSO-d6): 0.88 (3H, t), 1.00 (3H, t), 1.36 (4H, m), 1.88 (4H, m), 2.46 (4H, m), 2.70 (4H, m), 3.36 (4H, m), 4.28 (4H, m), 4.46 (1H, bs), 7.48 (1H, d), 7.80 (1H, d), 8.22 (1H, s), 9.27 (1H, s), 13.8 (1H, bs).

EXAMPLE 75

8-[5-(4-Hydroxypiperidine-1-sulphonyl)-2-propoxyphenyl]-6-pentyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (53%) from the title compound of Preparation 32 and 4-hydroxypiperidine following the procedure of Example 1.

MS: m/z 543 (M+1)+.

δ (DMSO-d6): 0.88 (3H, t), 1.00 (6H, m), 1.42 (6H, m), 1.82 (6H, m), 2.77 (2H, m), 3.17 (2H, m), 3.54 (1H, m), 4.26 (4H, m), 4.69 (1H, s), 7.46 (1H, d), 7.80 (1H, dd), 8.23 (1H, d), 9.26 (1H, s), 13.7 (1H, s).

EXAMPLE 76

3-(5-Oxo-6-pentyl-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]-purin-8-yl)-N-(2-piperidin-1-ylethyl)-4-propoxybenzene-sulphonamide

Obtained as a white solid (55%) from the title compound of Preparation 32 and 1-(2-aminoethyl)-piperidine following the procedure of Example 1.

MS: m/z 579 (M+1)+.

δ (DMSO-d6): 0.88 (3H, t), 0.98 (3H, t), 1.37 (6H, m), 1.60 (4H, m), 1.85 (4H, m), 2.60-3.43 (8H, m), 4.25 (4H, m), 7.45 (1H, d), 7.89 (1H, dd), 7.82 (1H, bs), 8.33 (1H, d), 9.26 (1H, s).

EXAMPLE 77

N-(2-Dimethylaminoethyl)-3-(5-oxo-6-pentyl-6,9-dihydro-5H[1,2,4]triazolo[3,4-i]purin-8-yl)-4-propoxybenzene-sulphonamide

Obtained as a white solid (38%) from the title compound of Preparation 32 and N,N-dimethylethylene-diamine following the procedure of Example 1.

MS: m/z 530 (M+1)+.

δ (DMSO-d6): 0.88 (3H, t), 0.99 (4H, m), 1.35 (4H, m), 1.85 (4H, m), 2.44 (1H, m), 2.44 (6H, s), 2.74 (2H, m), 2.99 (2H, m), 4.22 (4H, m), 7.45 (1H, d), 7.89 (1H, dd), 8.34 (1H, d), 9.26 (1H, s).

EXAMPLE 78

8-[5-(Morpholinosulphonyl)-2-propoxyphenyl]-6-pentyl-6,9-dihydro[1,2,4]triazolo[3,4-i]purin-5-one

Obtained as a white solid (30%) from the title compound of Preparation 32 and morpholine following the procedure of Example 1.

MS: m/z 529 (M+1)+.

δ (DMSO-d6): 0.90 (3H, t), 0.99 (3H, t), 1.37 (4H, m), 1.84 (4H, m), 2.89 (4H, m), 3.64 (4H, m), 4.22 (2H, t), 4.29 (2H, t), 7.49 (1H, d), 7.81 (1H, d), 8.22 (1H, s), 9.26 (1H, s), 13.75 (1H, bs).

The following Examples illustrate pharmaceutical compositions according to the present invention and procedures for their preparation.

PHARMACEUTICAL COMPOSITION: EXAMPLE 1

50,000 capsules each containing 100 mg of active ingredient were prepared according to the following formulation:

Active ingredient	5 kg
Lactose monohydrate	10 kg
Colloidal silicon dioxide	0.1 kg
Corn starch	1 kg
Magnesium stearate	0.2 kg

Procedure

The above ingredients were sieved through a 60 mesh sieve, and were loaded into a suitable mixer and filled into 50,000 gelatine capsules.

PHARMACEUTICAL COMPOSITION: EXAMPLE 2

50,000 tablets each containing 50 mg of active ingredient were prepared according to the following formulation:

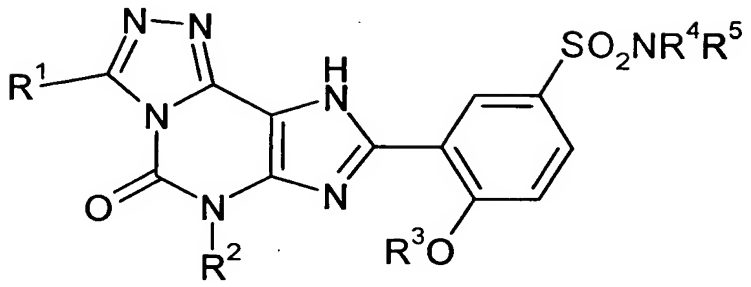
Active ingredient	2.5 kg
Microcrystalline cellulose	1.95 kg
Spray-dried lactose	9.95 kg
Carboxymethyl starch	0.4 kg
Sodium stearyl fumarate	0.1 kg
Colloidal silicon dioxide	0.1 kg

Procedure

All the powders were passed through a screen with an aperture of 0.6 mm, then mixed in a suitable mixer for 20 minutes and compressed into 300 mg tablets using 9 mm disc and flat bevelled punches. The disintegration time of the tablets was about 3 minutes.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1, R^2 and R^3 each independently represent: hydrogen; an alkyl group which is unsubstituted or substituted by a hydroxyl, alkoxy, alkylthio, amino, mono- or dialkylamino, hydroxycarbonyl, alkoxycarbonyl, acylamino, carbamoyl or alkylcarbamoyl group; or a group of formula

$$-(CH_2)_n-R^6$$

wherein n is a number from 0 to 4 and R^6 represents: a cycloalkyl group; a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, hydroxyl, alkylenedioxy, alkoxy, amino, mono- or dialkylamino, nitro, cyano or trifluoromethyl groups; or a 3- to 7- membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxyl, phenyl, alkoxycarbonyl, amino, monoalkylamino, dialkylamino or hydroxycarbonyl groups or one or more alkyl groups which may in turn be unsubstituted or substituted by one or more halogen atoms or hydroxyl, alkoxy, hydroxyalkoxy,

phenyl, alkoxycarbonyl, amino, mono- or dialkylamino or hydroxycarbonyl groups;

either R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 7- membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxyl, oxoalkyl, carbamoyl, hydroxycarbonyl, alkoxycarbonyl, amino, mono- or dialkylamino groups, or one or two alkyl groups which may be unsubstituted or substituted by one or more hydroxyl, alkoxy, hydroxyalkoxy, amino or mono- or dialkylamino groups, or

R^4 and R^5 independently represent a hydrogen atom or an alkyl group which may be unsubstituted or substituted by one or more hydroxyl, alkoxy, alkylthio, amino, mono- or dialkylamino groups, or

R^4 represents hydrogen or an alkyl group and R^5 represents a group of formula

$$-(CH_2)_n-R^7$$

wherein n is a number from 0 to 4 and R^7 represents: a cycloalkyl group; a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, hydroxyl, alkylenedioxy, alkoxy, amino, mono- or dialkylamino, nitro, cyano or trifluoromethyl groups; or a 3- to 7- membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxyl, alkoxy, phenyl, alkoxycarbonyl, amino, monoalkylamino, dialkylamino or hydroxycarbonyl groups or one or more alkyl groups which may be unsubstituted or substituted by one or more halogen atoms or hydroxyl, alkoxy, hydroxyalkoxy, phenyl, alkoxycarbonyl, amino, mono- or dialkylamino or hydroxycarbonyl groups;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 represents a hydrogen atom, a C_1-C_4 alkyl group or a group of formula

$$-(CH_2)_nR^6$$

wherein n is 0, 1 or 2 and R^6 represents a phenyl, pyridyl or morpholinyl group.

3. A compound according to claim 1 or 2 wherein R^2 and R^3 independently represent a C_1-C_4 alkyl group, a C_{3-10} cycloalkyl group, or a group of formula

$$-(CH_2)_nR^6$$

wherein n is 0, 1 or 2 and R^6 represents an unsubstituted or substituted phenyl group or a pyridyl group.

4. A compound according to any one of claims 1 to 3 wherein R^1 is a methyl, ethyl, propyl, pyridyl, pyridylmethyl, benzyl or *N*-morpholinylmethyl group; R^2 is an ethyl, propyl, n-butyl, substituted or unsubstituted benzyl or 3-pyridylmethyl group; and R^3 is an ethyl, propyl or n-butyl group.

5. A compound according to any one of claims 1 to 4 wherein the ring formed by R^4, R^5 and the nitrogen atom to which they are attached is a piperidyl, piperazinyl, [1,4]diazepine-1-yl, morpholinyl or pyrazolyl group which is unsubstituted or substituted by a group selected from a C_1-C_4 alkyl, carbamoyl, amino, hydroxyl, formyl hydroxy(C_1-C_4)alkyl groups and a hydroxy-alkoxyalkyl group wherein the alkyl moieties contain from 1 to 4 carbon atoms.

6. A compound according to claim 5 wherein R^4 and R^5 together with the nitrogen atom to which they are attached represent a 4-hydroxypiperidyl, 4-carbamoyl-

piperidyl, 3-carbamoylpiperidyl, piperazinyl, 4-methylpiperazinyl, 4-ethylpiperazinyl, 4-formylpiperazinyl, 4-methyl[1,4]diazepine-1-yl, 4-(2-hydroxyethyl)piperazinyl, 4-[2-(2-hydroxyethoxy)ethyl]piperazinyl, morpholinyl or aminopyrazolyl group.

7. A compound according to any one of claims 1 to 3 wherein R^4 and R^5 independently represent a hydrogen atom or a C_1-C_4 alkyl group which is unsubstituted or substituted by a hydroxyl or dimethylamino group.

8. A compound according to any one of claims 1 to 3 wherein R^4 is a hydrogen atom or a C_1-C_4 alkyl group and R^5 represents a group of formula

$$-(CH_2)_nR^7$$

wherein n is 0, 1, 2 or 3 and R^7 is a pyridyl, piperidyl, piperazinyl, morpholinyl, triazolyl or tetrazolyl group.

9. A compound according to any one of claims 1 to 8 characterized in that it has an IC_{50} value for the inhibition of PDE 5 of less than 30 nM.

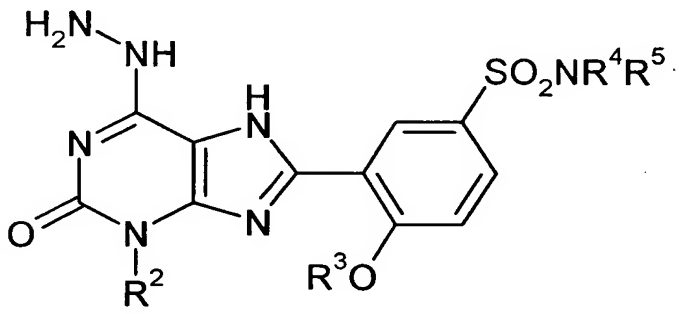
10. A compound according to claim 1 which is
6-ethyl-8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one,
8-[2-butoxy-5-(4-methylpiperazine-1-sulphonyl)phenyl]-6-ethyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one,
8-[5-(4-methylpiperazine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one,
8-{5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one,
8-[5-(4-methyl-[1,4]diazepine-1-sulphonyl)-2-propoxyphenyl]-6-propyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one,

6-butyl-8-{5-[4-(2-hydroxyethyl)piperazine-1-sulphonyl]-2-propoxyphenyl}-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one, and

3-(5-oxo-6-propyl-6,9-dihydro-5H[1,2,4]triazolo[3,4-*i*]purin-8-yl)-4-propoxy-*N*-pyridin-4-ylbenzene-sulphonamide;

or a pharmaceutically acceptable salt thereof.

11. A process for preparing a compound as defined in any one of claims 1 to 10, which process comprises reacting a hydrazinopurine derivative of formula (II)



(II)

wherein R^2, R^3, R^4 and R^5 are as defined in any one of claims 1 to 10, with a carboxylic acid of general formula (III):

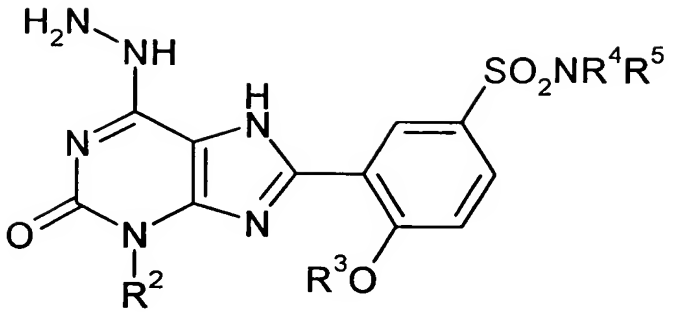
$$R^1—CO_2H$$

(III)

wherein R^1 is as defined in any one of claims 1 to 10, or a reactive derivative thereof optionally in the presence of a polar aprotic solvent.

12. A process according to claim 11 wherein said reaction is carried out in the presence of an organic base.

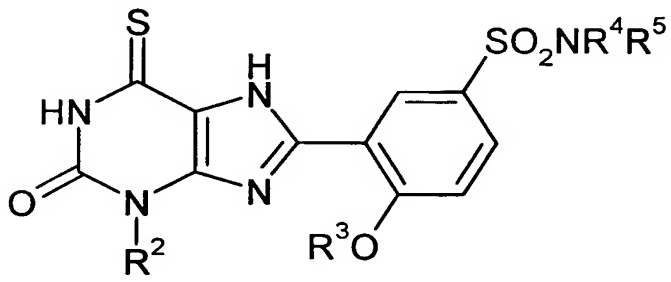
13. A compound of formula (II):



(II)

wherein R^2, R^3, R^4 and R^5 are as defined in claim 1.

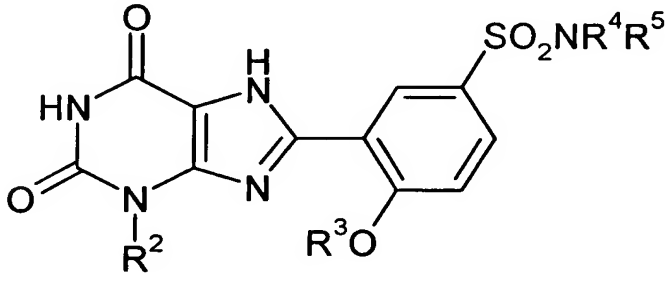
14. A compound of formula (IV):



(IV)

wherein R^2, R^3, R^4 and R^5 are as defined in claim 1.

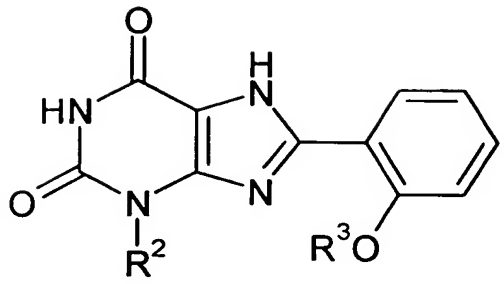
15. A compound of formula (V):



(V)

wherein R^2, R^3, R^4 and R^5 are as defined in claim 1.

16. A compound of formula (VI):

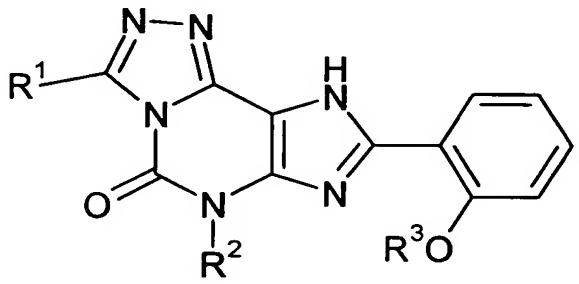


(VI)

wherein R^2 and R^3 are as defined in claim 1.

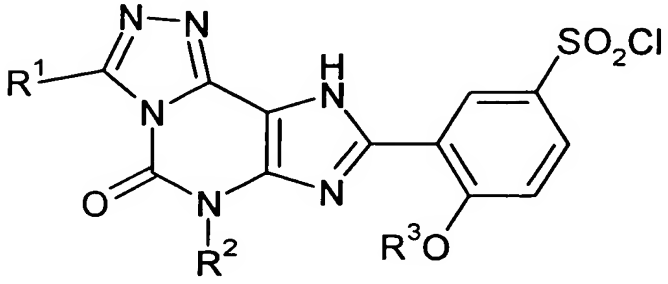
17. Use of a compound as defined in any one of claims 13 to 16 as an intermediate in the preparation of a compound as defined in claim 1.

18. A process for preparing a compound as defined in any one of claims 1 to 10, which process comprises reacting a phenylxanthine of formula (IX):



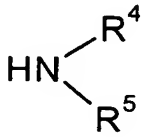
(IX)

wherein R^1, R^2 and R^3 are as defined in any one of claims 1 to 10, with chlorosulphonic acid so as to obtain the sulphonyl chloride of formula (X):



(X)

wherein R^1, R^2 and R^3 are as defined in any one of claims 1 to 10, and reacting the sulphonyl chloride of formula (X) with an amine of formula (VIII):



(VIII)

wherein R^4 and R^5 are as defined in any one of claims 1 to 10.

19. A process according to claim 13 wherein the reaction forming the sulphonyl chloride of formula (X) is carried out using an excess of chlorosulphonic acid or using the chlorosulphonic acid as a solvent, and the conversion of the sulphonyl chloride of formula (X) is carried out in a polar aprotic solvent and in the presence of an organic base.

20. A pharmaceutical composition comprising as active ingredient at least one compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

21. A compound according to any one of claims 1 to 10 or a composition according to claim 20 for use in a method of treatment of the human or animal body.

22. Use of a compound as defined in any one of claims 1 to 10 in the manufacture of a medicament for the treatment of stable, unstable or variant angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel potency, peripheral vascular disease, vascular disorders, thrombosis, bronchitis, chronic asthma, allergic asthma, allergic rhinitis,

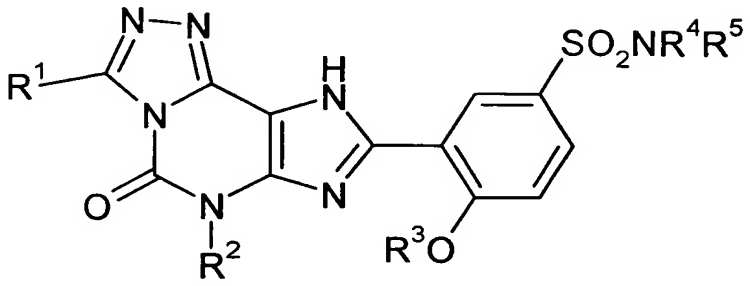
glaucoma, male erectile dysfunction, female sexual dysfunction or diseases characterized by disorders of gut motility.

23. A method of treating a human or animal body suffering from stable, unstable or variant angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel potency, peripheral vascular disease, vascular disorders, thrombosis, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, male erectile dysfunction, female sexual dysfunction or diseases characterized by disorders of gut motility, which method comprises administering to a patient requiring such treatment an effective amount of a compound as defined in claim 1.

ABSTRACT

8-PHENYL-6,9-DIHYDRO[1,2,4]TRIAZOLO[3,4-*i*]PURIN-5-ONE DERIVATIVES

8-Phenyl-6,9-dihydro[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives of formula (I):



(I)

wherein:

R^1, R^2 and R^3 each independently represent: hydrogen; a linear, branched or cyclic, substituted or unsubstituted, cycloaliphatic or aromatic, homocyclic or heterocyclic, organic group, R^4 and R^5 together with the nitrogen atom to which they are attached form a 3- to 7-membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted; or

R^4 and R^5 independently represent a hydrogen atom, or an alkyl group which may be unsubstituted or substituted, or

R^4 represents hydrogen or an alkyl group and R^5 represents a group of formula

$$-(CH_2)_n-R^7$$

wherein n is a number from 0 to 4 and R^7 represents: an organic group; or

R^4 and R^5 represent hydroxyl, alkoxy, hydroxy-alkoxy, phenyl, alkoxycarbonyl, amino, mono- or dialkyl-

amino or hydroxycarbonyl groups; or a pharmaceutically acceptable salt thereof; processes for their preparation, pharmaceutical compositions containing them and their use as PDE 5 inhibitors.